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REVIEW

Tularemia: a re-emerging tick-borne infectious disease

Derya Karataş Yeni[1] · Fatih Büyük[2] · Asma Ashraf[3] · M. Salah ud Din Shah[4]

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Abstract

Tularemia is a bacterial disease of humans, wild, and domestic animals. *Francisella tularensis*, which is a Gram-negative coccobacillus-shaped bacterium, is the causative agent of tularemia. Recently, an increase in the number of human tularemia cases has been noticed in several countries around the world. It has been reported mostly from North America, several Scandinavian countries, and certain Asian countries. The disease spreads through vectors such as mosquitoes, horseflies, deer flies, and ticks. Humans can acquire the disease through direct contact of sick animals, consumption of infected animals, drinking or direct contact of contaminated water, and inhalation of bacteria-loaded aerosols. Low infectious dose, aerosol route of infection, and its ability to induce fatal disease make it a potential agent of biological warfare. Tularemia leads to several clinical forms, such as glandular, ulceroglandular, oculoglandular, oropharyngeal, respiratory, and typhoidal forms. The disease is diagnosed through the use of culture, serology, or molecular methods. Quinolones, tetracyclines, or aminoglycosides are frequently used in the treatment of tularemia. No licensed vaccine is available in the prophylaxis of tularemia and this is need of the time and high-priority research area. This review mostly focuses on general features, importance, current status, and preventive measures of this disease.

Keywords *Francisella tularensis* · Tularemia · Vector-borne infection

Abbreviations

ASM	American Society for Microbiology
AVMA	American Veterinary Medical Association
CDC	Centers for Disease Control and Prevention
ECDC	The European Centre for Disease Prevention and Control
GIDEON	Global Infectious Diseases and Epidemiology Network
LVS	Live vaccine strain
MALDI-ToF MS	Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry
MLVA	Multilocus VNTR analysis
TBD	Tick-borne disease
USA	United States of America
USSR	Union Soviet Socialist Republics

Introduction

Francisella tularensis is a pleomorphic, Gram-negative, non-motile, and non-spore-forming intracellular bacterium. It was isolated for the first time in Tulare county of California in 1911. Tularemia is also known as Pahvant Valley plague, rabbit fever, deer fly fever, and Ohara's fever. The causative organism of tularemia has been isolated from man and a wide range of animal species including mammals, birds, fishes, amphibians, arthropods, and protozoa. It is also revealed that isolation of this bacterium may represent colonization without infection as the presence of the organism has been reported from animals without any disease symptoms. *F. tularensis* is taxonomically divided into several sub-species, including *tularensis* (also known as type A), *holarctica* (also known as type B), *mediaasiatica*, and *novicida*. Cottontail rabbits (*Sylvilagus* spp.) and ticks are the main reservoirs of type A (Telford and Goethert 2020). On the other hand, aquatic

✉ Fatih Büyük
fatihbyk08@hotmail.com

[1] Veterinary Control Central Research Institute, Bacterial Disease Laboratory, Ankara, Turkey

[2] Department of Microbiology, Veterinary Faculty, University of Kafkas, Kars, Turkey

[3] Department of Zoology, Government College University, Faisalabad, Pakistan

[4] Nuclear Institute for Agriculture and Biology (NIAB), Faisalabad, Pakistan

rodents (muskrats and beavers) are believed to spread type B. The terrestrial cycle of type A strains and aquatic cycle of type B strains have been described in the USA, but remain debated (Hansen et al. 2011). They cannot be extrapolated to the rest of the world. In fact, terrestrial and aquatic cycles can also be found in Europe and Asia, where only type B strains are found (Carvalho et al. 2014). In human cases, type A is found more virulent than type B (Mörner 1992; Ellis et al. 2002). Transmission of *F. tularensis* to humans is through the handling of infected animals, consumption of contaminated food or water, vector bites (ticks, flies, and mosquitoes), contact with aquatic environment, and inhalation of aerosols (Hopla 1974; Pearson 1998). The clinical manifestation of tularemia depends on the route of acquisition. A conspicuously enlarged tender node arises when bacteria are acquired through the skin or oral mucous membranes. Inhalation of *F. tularensis* primarily results in pneumonia, which may be associated with deep mediastinal lymphadenopathy (Anda et al. 2007).

Tularemia has been reported in most countries of the northern hemisphere and most frequently in the Scandinavian countries, northern America, Japan, and Russia. The incidence is high especially in North America and the Nordic countries. Moreover, tularemia has recently been reported from Turkey, Yugoslavia, Spain, Kosovo, and Switzerland. In countries with a relatively high incidence of the disease, the geographical distribution is uneven. The reasons underlying the geographical restriction of outbreaks are not known. However, this is probably due to increased awareness and improved diagnosis rather than to the global spread of the bacterium. Ultimately, tularemia is thought to be more widely distributed than was previously thought (Sjöstedt 2007b; Gürcan 2014).

Tularemia is a zoonotic disease and rodents, hares, and rabbits are important sources of human infection (Mörner 1992). Tularemia has recently become a significant re-emerging disease in the world because of the important role of bacteria in biological terrorism agents. The low infectious dose, easy and high dissemination with aerosols, and ability to induce fatal disease make *F. tularensis* a potential agent of biological warfare. Hence, tularemia has been classified by the Centers for Disease Control and Prevention (CDC) as a category A biological weapon (Dennis et al. 2001; Maurin 2015).

Etiology

Francisella tularensis is the causative agent of tularemia. The bacterium is an aerobic, Gram-negative, intracellular organism, having bipolar morphology. It harbors a cell wall rich in fatty acids and besieged by a semi-virulent capsule. The *Francisella* genus could be divided into two main genetic clades; one including *F. tularensis*, *F. novicida*, and *F. hispaniensis*, and another including *F. philomiragia* and *F. noatunensis* (Sjödin et al. 2012). *F. tularensis* is one of the members of *Francisella* genus in terrestrial animals and contains four subtypes. These are *F. tularensis* subsp. *tularensis* (type A), *F. tularensis* subsp. *holarctica* (type B), *F. tularensis* subsp. *novicida*, and *F. tularensis* subsp. *mediaasiatica*. Among these, *F. tularensis* subsp. *tularensis* and *F. tularensis* subsp. *holarctica* are considered major etiological agents of tularemia in humans. While *F. tularensis* subsp. *novicida* is very rarely associated with human infections (Sjöstedt 2005), human infection due to *F. tularensis* subsp. *mediaasiatica* has never been documented in the published literatures.

F. tularensis subsp. *tularensis*

F. tularensis subsp. *tularensis* is the causative agent of type A tularemia, which presents exclusively in North America. Type A is a more virulent subspecies of the microorganism, which is responsible for the majority of infections in humans (Pilo 2018). This disease is also known as rabbit fever because it was mostly found in hunters of rabbits and hares. Rabbits (*Sylvilagus* spp.) and hares (*Lepus* spp.) were found to be the carriers/reservoirs of *F. tularensis* subsp. *tularensis* (Sjöstedt 2007a). The emergence of tularemia occurred in the USA with the import of the rabbits (*Sylvilagus floridanus*) in the late 1950s. Initially, few cases were reported in the USA then it became an endemic disease (Belding and Merrill 1941). Tularemia was much more common in the USA in the early part of the twentieth century. Tularemia, which had almost 1000 cases annually in the 1950s, is now around 250 cases annually (Center for Disease Control and Prevention 2018). *F. tularensis* subsp. *tularensis* is divided into 2 distinct subpopulations as A.I. (A-east) and A.II. (A-west) by MLVA analysis, considering the geographic distribution, disease outcome, and transmission. A.I. occurs primarily in the central and eastern United States, while A.II. occurs primarily in the western United States. Moreover, it is suggested that A.II. infections are less severe than either type B or A.I. infections (Johansson et al. 2004; Staples et al. 2006).

F. tularensis subsp. *holarctica*

In Europe, *F. tularensis* subsp. *holarctica* is the leading cause of tularemia. Moreover, it has also been reported from North America (Mörner and Addison 2001). Tularemia is primarily a zoonotic disease; most human infections occur through direct or indirect contact with infected animals. Arthropod-borne and water-borne infections are less frequent except in specific areas, e.g., Sweden and Turkey (Ohlin 1942; Kılıç et al. 2015). Outbreaks mostly occur initially in rodents followed by the epidemics in humans. It was also found that the voles (*Microtus* spp.) and water voles (*Arvicola terrestris*) are the carriers/reservoirs of *F. tularensis* subsp. *holarctica*

(Olsuf'ev and Shlygina 1979). Water reservoirs are among major sources of infection as the infected voles excrete the bacteria in urine and contaminate the water (Bell and Stewart 1975). Water-borne infection of *F. tularensis* subsp. *holarctica* is more important in humans compared with the vector-borne disease because mostly the disease spreads in humans through contact with contaminated water or infected animals (Reintjes et al. 2002).

Tick-borne tularemia cases are found in almost all disease endemic areas but tularemia cases occurring through flies or mosquitoes bites have only been reported from specific geographic areas. Important vectors responsible for the spread of *F. tularensis* subsp. *holarctica* are hard ticks (*Ixodidae*), biting flies, and mosquitoes. In Europe, important tick vectors are *D. nuttalli*, *D. marginatus*, *I. ricinus*, *D. reticulatus*, and *Hymaphysalus concinna* (Gurycova et al. 1995). An outbreak in humans was reported from Sweden and Finland. It was found during investigations that wild rodents were carriers of the pathogen while mosquitoes were acting as a vector in the spread of the disease (Eliasson et al. 2002). Spread of the disease through mosquitoes can also be possible by infection of mosquitoes at the larval stage from the contaminated aquatic environment and transstadial transmission of *F. tularensis* up to the adult stage. Moreover, different species of mosquitoes (*Aedes*, *Culex*, and *Anopheles*) can be involved in the spread of disease (Petrishcheva 1965).

Epidemiology

Species susceptibility of *F. tularensis*

Francisella tularensis is a bacterium with such a wide host range that (Hopla and Hopla 1994) made a well-fitted definition for it as "Few, if any, zoonotic disease agents have a broader host distribution than *F. tularensis*." So, indeed, the organism is deserving of this definition since it infects more than 100 species of wild and domestic vertebrates and over 100 species of invertebrates. The most important vertebrates, which are assumed as the primary vectors of *F. tularensis*, are Lagomorpha, Rodentia, and Sciuromorpha. Lagomorphs (cottontail rabbits), hares, jackrabbits, muskrats, beavers, and a variety of rodents such as voles, field, mice, squirrels, and lemmings are common wild animal hosts of the organism. Among domestic animals, tularemia occurs in sheep, cats, rabbits, dogs, pigs, and horses. Birds are considered resistant to tularemia but a variety of species has acquired natural infections. The more striking of that is a description about the infection with *F. tularensis* in two birds of prey (a rough-legged buzzard (*Buteo lagopus*) and a Ural owl (*Strix uralensis*)) in Sweden (Mörner and Mattsson 1983). The other was just an assumption that the birds may act as a vector, carrying the *F. tularensis* on their claws or beak without any infection that was asserted following the attack of common buzzards (*Buteo buteo*) on some jogger people in the Kanton Aargau in Switzerland (Ehrensperger et al. 2018).

Routes of transmission

Transmission of *F. tularensis* to humans is through the handling of infected animals, consumption of contaminated food or water, vector bites (such as ticks, flies, and mosquitoes), contact with aquatic environment, and inhalation of aerosols (Hopla 1974; Pearson 1998). Therefore, it is also noticed that the disease was found mostly in humans working/living close to animals and agricultural lands (Berdal et al. 1996; Eliasson et al. 2006). *F. tularensis* can be transmitted to humans via the skin when they handled infected or live animals' tissue, skin, or blood. Eating undercooked animal tissues or foods and consumption of water that have been contaminated by infected carcasses or excretions can infect people. Some human infections with *F. tularensis* were linked to immersion in water. Respiratory infections sometimes occur in agricultural occupations such as piling hay or mowing lawns especially running over infected animals or carcasses. Arthropod vectors such as ticks, biting flies, and mosquitoes are also important in the transmission of tularemia to humans. Person-to-person transmission has not been reported. The enter site and transmission route of infection determine the clinical form of the disease.

Role of vectors in transmission

The infection is transmitted among mammalian hosts by a variety of arthropod vectors. In the case of USA, most common vectors are biting flies in Utah, Nevada, and California, while ticks are the most important vectors around the Rocky Mountains (Ellis et al. 2002). In the former Soviet Union, it was reported that both mosquitoes (*Aedes*, *Culex*, and *Anopheles*) and ticks (*Ixodes*) transmit the infection (Ellis et al. 2002). In Japan, no arthropod-borne cases were reported before 1951, whereas several arthropod-borne cases were reported between 1972 and 1998. The disease reported to spread during winter by direct contact with infected hares was biphasic. Moreover, arthropod-borne cases were reported mostly from spring to autumn (Ohara et al. 1998). In Central Europe, *D. reticulatus* and *I. ricinus* ticks were reported as important vectors for transmission of the disease (Hubalek et al. 1996; Hubalek et al. 1998). It was also observed that during an outbreak, mosquito bites could be the major risk factor for the rapid spread of the disease (Eliasson et al. 2002).

Water as a source of tularemia

Francisella tularensis can survive and infectivity persists in water sources through amoebae and primary hosts such as

beavers, muskrats, or lemmings (Gürcan 2014). The contamination of waters is primarily due to urine and feces from infected animals or the carcasses of animals dying from tularemia. It is experimentally estimated that one infected water vole or mouse can contaminate up to 500,000 l of water with *F. tularensis* (Pavlovsky 1966). The organism can survive at infective levels in water for more than a month and may become an important vehicle for contamination or infection of biting insects, vertebrate animals, and humans. Water-borne tularemia outbreaks and sporadic cases have been reported worldwide in the last decades. These infections represent a major public health and military challenge. Humans can be infected by *F. tularensis* through not only consumption the water but also use of contaminated water and various aquatic activities such as swimming, canyoning, and fishing. Water-borne tularemia was first described in the 1930s in the USSR (Karpoff and Antonoff 1936). However, it gained momentum as usual and the cases linked with drinking water increased in the last 20 years in many countries such as Turkey, Kosovo, Bulgaria, Georgia, Norway, Sweden, Italy, and Germany. In Turkey, all human cases originated from water sources and all of these are almost related to consumption of drinking water. Large outbreaks affecting more than hundreds of peoples have been reported in Kosovo and Bulgaria which were eventually linked with the water sources. Similarly, tens of human cases originated from the water sources have been reported in Georgia, Macedonia, and Norway (Kılıç et al. 2015; Hennebiquea et al. 2019).

Geographical distribution

Tularemia has been reported in many countries of the world since it was first reported in the USA. The incidence of tularemia has changed from 0.37 to 2.8/one million cases per year over the past 50 years in the USA. Although, a decrease is seen after the 1950s, it tended to emerge in 2015 and beyond in the USA (CDC 2018). *F. tularensis* subsp. *tularensis* is the most virulent subspecies which accounts for approximately 90% of human infections in North America (Şahin 2009; Grunow et al. 2012). Mostly, the American cases of tularemia in humans were reported during summer and fall seasons because its relation with arthropod acts like bites from infected ticks or flies. However, infections due to animal handling and hunting can occur at any time of the year. Canada is the other country where tularemia is endemic in North America (Table 1).

Tularemia is widely distributed throughout European countries. It can be said that it followed a fluctuant course between 1995 and 2017 (GIDEON 2019). The total number of confirmed cases per one hundred thousand people ranged from 0.1 to 0.06 between 2014 and 2018 (ECDC 2019). Especially, some of the Nordic countries (Finland and Sweden) are ascribed as endemic areas for tularemia. In these territories, tularemia is typically transmitted by mosquito bites. More recently, a tularemia outbreak, which is the biggest epidemic for more than 50 years, has been linked with mosquito bites in Sweden in 2019 (Dryselius et al. 2019). Tularemia is also occurring in Eastern Europe and Russia. Outbreaks in these regions increased after the Second World War. Kosovo reports the highest annual incidence of tularemia in Europe at a rate of 5.2 per 100,000 (Grunow et al. 2012). However, case number has not decreased lately in Kosovo (Sadiku et al. 2015; GIDEON 2018). Tularemia shows a seasonal pattern in these countries with relatively cold climates, with most cases occurring from July to November, which is consistent with a higher likelihood of exposure to the organism or vectors due to recreational outdoor activities. Albania, Greece, Iceland, UK, Ireland, and Liechtenstein are some of the European countries known as free from human tularemia (Table 1). Tularemia is occurring in parts of Asia. Cases have been reported in China and Japan, which represent the Eastern part of the Asia continent. Iran and Turkey are the members of Western Asia countries where human tularemia cases have been reported. The Caucasus nations, Armenia and Azerbaijan, are the other countries that regularly report cases. In certain countries, the ingestion of contaminated water is the main transmission route of the disease: one such example is Turkey. A majority of the cases have been reported from rural or semirural areas of Turkey (Ogden et al. 2014), mostly during late summer or early autumn season (Orkun et al. 2014). Kazakhstan, Uzbekistan, and Turkmenistan are the regions that tularemia has been reported in Central Asia (Table 1) (Olsufiev 1977; Oyston and Quarry 2005).

Currently, Africa and South America are considered free of tularemia. While some cases of the disease were reported from Sudan and Kenya, they need confirmation through standard methods. Recently, few reports have been made from Australia and these cases have been confirmed by culture method (Table 1). Kenya has an exceptional situation; due to the lack of reliable laboratory diagnostic facilities and the presumptive clinical management of diseases coursing with fever such as tularemia, it is likely to be misdiagnosed. However, the researchers may have unwillingly reported an acute infection in patients rather than a sole serosurvey. Namely, they have used an ELISA kit that allows detecting all classes of antibodies (one of these, IgM, represents the acute form of the disease) to the lipopolysaccharide of *F. tularensis* in human serum. Moreover, the patients tested have shown some common clinical presentations of tularemia such as lymphadenopathy, generalized body aches, malaise/fatigue, and sore throat (Nejeru et al. 2017).

Symptoms

The incubation period of tularemia is usually from 3 to 5 days, but it can extend up to 14 days. The generalized symptoms of

Table 1 The global distribution of tularemia

Continent/country/region		Distribution	References
			Africa
Algeria	Côte d'Ivoire	Absent, no presence record(s)	(OIE Handistatus 2005; OIE 2009)
Botswana	Lesotho		
Cabo Verde	Libya		
Central African Republic	Madagascar		
Democratic Republic of the Congo	Mauritius		
Réunion	Tanzania		
Rwanda	Tunisia		
São Tomé and Príncipe	Zambia		
Seychelles	Zimbabwe		
South Africa	Malaysia		
Kenya		Present	(Nejeru et al. 2017; GIDEON 2019)
Sudan			(Mohamed Salma et al. 2012)
			Asia
Armenia		Present	(Melikjanyan et al. 2017; GIDEON 2019)
Azerbaijan			(GIDEON 2019)
Bahrain	Indonesiai	Absent, no presence record(s)	(OIE Handistatus 2005; OIE 2009)
Bangladesh	Kuwait		
Bhutan	Kyrgyzstan		
Brunei	Lebanon		
Malaysia	Pakistan		
Nepal	Singapore		
North Korea	Sri Lanka		
Oman			
China		Present	(Wang et al. 2014)
Georgia			(Elashvili et al. 2015; Hennebiquea et al. 2019)
Iran			(Esmaeili et al. 2014; OIE 2009; Zargar et al. 2015)
Israel			(World Health Organization-WHO 2007)
Japan			(Nakamura et al. 2018)
Kazakhstan			(Olsufiev 1977; Oyston and Quarry 2005; GIDEON 2019)
South Korea			(Ohara et al. 1998; GIDEON 2019)
Syria			(Ohara et al. 1998; GIDEON 2019)
Taiwan			(CDC 2018)
Tajikistan			(Ohara et al. 1998; GIDEON 2019)
Turkey			(Erdem et al. 2014; Büyük et al. 2016; GIDEON 2019)
Turkmenistan			(Olsufiev 1977)
United Arab Emirates			(Ohara et al. 1998; GIDEON 2019)
Uzbekistan			(Ohara et al. 1998; Oyston and Quarry 2005; GIDEON 2019)
			Europe
Albania	Iceland	Absent, no presence record(s)	(OIE Handistatus 2005; OIE 2009; ECDC 2019)
Andorra	Ireland		
Greece	Isle of Man		
Jersey	Malta		
Liechtenstein	Montenegro		
Luxembourg			
Austria		Present	(ECDC 2019)

Table 1 (continued)

Continent/country/region		Distribution	References
Belgium			(ECDC 2019)
Bosnia and Herzegovina			(GIDEON 2019)
Bulgaria			(OIE 2009; Padeshki et al. 2010; ECDC 2019; GIDEON 2019)
Croatia			(OIE 2009; Gürcan 2014; ECDC 2019)
Cyprus			(Uncu et al. 2017)
Czechia			(Hubálek and Halouzka 1997; OIE 2009; Gürcan 2014; ECDC 2019)
Denmark			(Byström et al. 2005; Haulrig et al. 2020)
Estonia			(ECDC 2019)
Finland			(Syrjala et al. 1985; OIE 2009; Rossow et al. 2014; ECDC 2019)
France			(Decors et al. 2011; Maurin et al. 2011; ECDC 2019)
Germany			(Kaysser et al. 2008; OIE 2009; Müller et al. 2013; Robert Koch Ins. 2017; ECDC 2019)
Hungary			(OIE 2009; Gyuranecz et al. 2012; ECDC 2019)
Italy			(ECDC 2019)
Latvia			(ECDC 2019)
Lithuania			(ECDC 2019)
Netherlands			(ECDC 2019; GIDEON 2019)
Macedonia			(GIDEON 2019)
Norway			(Berdal et al. 1996; OIE 2009; Nordstoga et al. 2014; ECDC 2019; GIDEON 2019)
Poland			(OIE 2009; Moniuszko et al. 2011; ECDC 2019)
Portugal			(Lopes de Carvalho et al. 2018; ECDC 2019)
Romania			(ECDC 2019; GIDEON 2019)
Russia			(Sandström et al. 1992; Efimov et al. 2003; OIE 2009; GIDEON 2019)
Serbia			(GIDEON 2019)
Slovakia			(Guryčová et al. 2001; OIE 2009; Gürcan 2014; ECDC 2019)
Slovenia			(ECDC 2019)
Spain			(Anda et al. 2001; García del Blanco et al. 2004; OIE 2009; ECDC 2019)
Sweden			(Mörner et al. 1988; OIE 2009; Rydén et al. 2011; Dryselius et al. 2019; GIDEON 2019)
Switzerland			(Friedl et al. 2005; OIE 2009)
Ukraine			(GIDEON 2019)
UK			(ECDC 2019)
			North America
Barbados	Cuba	Absent, no presence record(s)	(OIE Handistatus 2005; OIE 2009)
Bermuda	Curaçao		
British Virgin Islands	Dominica		
Cayman Islands	Dominican Republic		
Costa Rica	El Salvador		
Greenland	Nicaragua		
Guatemala	Panama		
Haiti	Saint Kitts and Nevis		
Honduras	Saint Vincent and the Grenadines		
Mexico	Trinidad and Tobago		
Canada		Present	

Table 1 (continued)

Continent/country/region			Distribution	References
				(OIE 2009; Wobeser et al. 2009; Blackburn et al. 2013; GIDEON 2019)
USA			Present	(Geiger 1931; Jellison et al. 1965; Evans et al. 1985; Magee et al. 1989; Taylor et al. 1991; Gliatto et al. 1994; Shoemaker et al. 1997; Lindley et al. 2002; Avashia et al. 2004; Magnarelli et al. 2007; O'Toole et al. 2008; Sinclair et al. 2008; OIE 2009; Calanan et al. 2010; Scheftel et al. 2010; Hansen et al. 2011; Brett et al. 2014; Larson et al. 2014; CDC 2018; GIDEON 2019)
- Alabama	- Colorado	- Illinois		
- Alaska	- Connecticut	- Indiana		
- Arizona	- Delaware	- Iowa		
- Arkansas	- Florida	- Kansas		
- California	- Idaho	- Kentucky		
- Louisiana	- Missouri	- New Jersey		
- Maryland	- Montana	- New Mexico		
- Massachusetts	- Nebraska	- New York		
- Michigan	- Nevada	- North Carolina		
- Minnesota	- New Hampshire	- North Dakota		
- Ohio	- South Dakota	- Virginia		
- Oklahoma	- Tennessee	- Washington		
- Oregon	- Texas	- West Virginia		
- Pennsylvania	- Utah	- Wisconsin		
- South Carolina	- Vermont	- Wyoming		
			Oceania	
Australia -Northern Territory -Tasmania			Present	(Whipp et al. 2003; OIE 2009; Siddaramappa et al. 2011; Jackson et al. 2012)
French Polynesia New Caledonia New Zealand	Samoa Vanuatu		Absent, No presence record(s)	(OIE Handistatus 2005; OIE 2009)
			South America	
Argentina Bolivia Brazil Falkland Islands Guyana Paraguay	Chile Colombia Ecuador Peru Uruguay Venezuela		Absent, no presence record(s)	(OIE Handistatus 2005; OIE 2009)

tularemia include fever along with malaise, chills, and headache. However, tularemia has six classical forms in humans, including ulcero-glandular, glandular, pneumonic, oro-pharyngeal, oculo-glandular, and systemic. Mostly, the site and route of infection determine the clinical form of the disease. Infection through ingestion of the bacterium typically results in the oro-pharyngeal form of the disease and symptoms such as pharyngitis, fever, and cervical lymphadenitis appear (Penn 1994). Infection by direct contact with an infected animal or a vector bite results in the ulcero-glandular form of tularemia having symptoms of skin lesions and lymphadenopathy. Although the glandular tularemia resembles the ulceroglandular form in terms of transmission, it differs with the presence of regional lymphadenopathy without any detectable skin lesion. The oculo-glandular form often develops through contact of contaminated hands, a splash of infected animal's body fluids into the conjunctiva, or direct contact

with contaminated water. The pneumonic form develops as the result of the inhalation of infectious aerosols. Moreover, pneumonic form and typhoidal forms of tularemia are considered systemic forms as they develop by the spread of bacteria through blood circulation as a systemic disease. The systemic forms (pneumonic and typhoidal) of the most virulent type A.I strain of tularemia have a high mortality rate (up to 60%) in the USA (Plourde et al. 1992). Only generalized signs have been reported in cases of the typhoidal form of the disease. Besides these well-characterized clinical forms, tularemia can also cause secondary pleuropneumonia, meningitis, and sepsis, which can lead to shock and death in humans (AVMA 2003).

Diagnosis

The diagnosis of tularemia mostly relies on positive serology in combination with clinical and epidemiological contexts. Tularemia is suspected when fever along with lymphadenopathy is reported in a patient, especially with a history of contact with animals, e.g., rabbit, deer, or ticks. However, its differential diagnosis from Q fever, plague, and psittacosis is required. Microagglutination test or ELISA (Grunow et al. 2000; Büyük et al. 2016) can detect serum antibodies against *F. tularensis*. However, the cross-reactivity has been reported with *Salmonella*, *Brucella*, *Legionella*, and *Yersinia* spp. (Karataş Yeni and İzgür 2015a). It is supposed that a 4-fold rise in anti-Francisella serum antibody titer within 2–4 weeks confirms the presence of tularemia infection (Karataş Yeni and İzgür 2015b).

Francisella tularensis is a biohazardous pathogen; therefore, specially equipped laboratories and skilled laboratory personnel are required for culture and diagnosis of tularemia. Isolation of the bacteria should be done in Biosafety Level 3 laboratories (ASM 2016). Therefore, the diagnosis of the pathogen through culture methods is difficult and not common ($\leq 10\%$). Microbiological techniques include culturing of the causative organism from the samples. Being a strict aerobe, *F. tularensis* requires a special medium with supplementation of sulfhydryl compounds for its optimal growth. It requires cysteine-enriched media, e.g., cysteine heart agar with red blood cells or cysteine glucose blood agar. Gray colonies having 4-mm diameter are reported on glucose cysteine blood agar along with the color change of the medium to green. Colony morphology may vary with strains. The best incubation temperature for its optimal growth is 35 °C. Moreover, colonies appear in 2 to 4 days of incubation. Mouse inoculation test can also be performed which results in the death of experimental mice. Fluorescent antibody staining of exudate or cultured bacteria enhances the detection sensitivity of direct smears.

Polymerase chain reaction (PCR)-based methods are useful when tissue samples are available. Presence of the *F. tularensis* in infected tissues can be confirmed by amplification of target sequences of nucleic acids using specific primers (Forsman et al. 1994; Keim et al. 2007). A new technique, MALDI-ToF mass spectrometry, is recently evaluated as a useful tool for rapid identification and typing of the isolated *F. tularensis* strains. Accuracy of this analysis highly depends on available mass spectrum databases. However, MALDI-ToF MS-analysis provides results in accordance with the PCR assay (Afanas'ev et al. 2015; Karatuna et al. 2016).

Treatment

Antimicrobial therapy should be applied to prevent complications in *F. tularensis* infections, to shorten the recovery period and to decrease mortality. Aminoglycosides, tetracyclines, quinolones, and chloramphenicol are frequently used in the treatment of tularemia (Tärnvik and Chu 2007; Sjöstedt 2016). Resistance against penicillins, cephalosporins, carbapenems, macrolides, and clindamycin has been reported (Kılıç and Yeşilyurt 2011; Origgi et al. 2014). Moreover, higher relapse rates are also reported after antimicrobial therapy. So, aminoglycosides are usually administered for 10 days, fluoroquinolones for 14 days, and doxycycline for 21 days to avoid the relapse (Caspar and Maurin 2017).

The treatment approach depends on the severity of the infection. For example, in severe infection, such as prolonged or extensive systemic symptoms, sepsis with or without renal failure, typhoidal tularemia, and symptomatic pneumonic tularemia, the aminoglycosides (gentamycin and streptomycin) are the drugs of the first choice (Enderlin et al. 1994; Johansson et al. 2002). Successful outcomes have been reported in the use of aminoglycosides in the treatment of complications of tularemia such as meningitis and endocarditis with the combination of tetracycline, chloramphenicol, and ciprofloxacin (Barbaz et al. 2013). Gentamicin is the preferred aminoglycoside for the treatment of tularemia in children; however, streptomycin is used to eliminate the gentamicin failures (Kaya et al. 2011). Ciprofloxacin and doxycycline are recommended drugs for mild or moderate infection in adults. These two drugs and chloramphenicol combined with an aminoglycoside can be used for the management of meningitis and endocarditis (Barbaz et al. 2013). Azithromycin represents a first-line treatment option for tularemia during pregnancy by overcoming the side effects of gentamicin and ciprofloxacin (Dentan et al. 2013; Johnsrud et al. 2019). The treatment of immunosuppressed patients with tularemia is proven with the use of gentamicin, a fluoroquinolone, or doxycycline, alone or in combination (Ozkok et al. 2012; Alias et al. 2017).

The duration of treatment for tularemia ranges 10 to 14 days. However, the duration of the treatment can be shortened in cases in children to 7 days or extended to 21 days in cases of meningitis and endocarditis (Gaci et al. 2017). The post-exposure prophylaxis differs between adults and children. This depends on the

type of exposure and the length of time since the exposure. Regimens for adults are oral ciprofloxacin (500 mg) or doxycycline (100 mg), each twice daily for 14 days. The recommended doses for children are ciprofloxacin (15 mg/kg) orally twice daily or doxycycline (2.2 mg/kg) orally twice daily (for those < 45 kg), and 100 mg orally twice daily (for those ≥ 45 kg) (Dennis et al. 2001).

Prevention

Individuals can easily protect themselves by adapting the following precautionary measures that would minimize the risk of exposure to the organism (Sjöstedt 2007a; WHO 2007).

1. Avoid drinking, bathing, swimming, or working in untreated water where infection may be common among wild animals.
2. Use impervious gloves and clothes when skinning, handling, or dressing wild animals, especially rabbits.
3. Cook the meat of wild rabbits and rodents thoroughly.
4. Use insect repellents.
5. Protect food warehouses from contact with vector animals.
6. Wear protective masks against infected dust and aerosols if you are a member of the professional group, such as farmers or gardeners.
7. Avoid being bitten by deer flies and ticks.
8. Check your clothing often for ticks climbing toward open skin. Wear white or light-colored long-sleeved shirts and long pants so the tiny ticks are easier to see. Tuck long pants into your socks and boots. Wear a head covering or hat for added protection.
9. Walk in the center of trails so weeds do not brush against you.
10. If you let your pets outdoors, check them often for ticks. Infected ticks can also transmit tick-borne diseases to them. Check with your veterinarian about preventive measures against tick-borne diseases. You are also at risk from ticks that "hitch a ride" on your pets but fall off in your home.
11. Make sure the property around your home is unattractive to ticks. Keep your grass mowed and keep weeds cut.
12. The person or veterinarian working in close contact with the rabbits or suspected animals should be vaccinated against the pathogen.

Vaccines against tularemia

Currently, no vaccine against tularemia is available or approved for humans. However, efforts have been done to develop vaccines (killed and attenuated) against tularemia. Killed in this manner, live attenuated and subunit vaccine candidates were evaluated in several countries. Apart from an effective attenuated vaccine that was lost unintentionally (Tigertt 1962), other vaccines have not yielded promising results for protective immunity (Titball and Sjostedt 2003; Conlan 2004; Valentino et al. 2009). At the end of all these studies, it was suggested that different requirements for protective vaccines against each subtype of *F. tularensis* are required and the attenuation and protective ability of a vaccine should be adjusted in a delicate balance (Barry et al. 2009). Furthermore, due to the intracellular adaptation of *F. tularensis*, the new vaccine development initiatives should aim to provide outstanding cell-mediated immunity for long-term protection (Sjöstedt 2007a).

An agent of biological warfare

Having low infectious dose and easy dissemination of the agent high aerosol-related infection rate and ability to induce fatal disease makes *F. tularensis* a potential agent of biological warfare. The US Department of Health and Human Services classified it as a List A select agent of the highest concern of bioterrorism use. Indeed, there were some certain reports about the use of *F. tularensis* as a biological weapon by Japan, Russia, and Germany during World War II (Dennis et al. 2001).

The Former Soviet Union developed the drug-resistant *F. tularensis*, weaponized, and stockpiled it until the 1960s. World Health Organization warned about the deaths of 19,000 persons in case of use of *F. tularensis* as a biological weapon in a city having a population of 5 million people (Christopher et al. 1997). Centers for Disease Control and Prevention (CDC) estimated a treatment cost of about 5.4 billion US dollar for every 100,000 persons exposed to the agent (Dennis et al. 2001). In case of an attack of a biological weapon having *F. tularensis*, important factors to minimize the losses are the ability to make a rapid diagnosis, its differentiation from environmental strains, and availability of effective drugs or vaccines.

Future perspectives

The countries having natural conditions favorable for tick-borne infections in animals and humans need to develop a disease management strategy and establish control programs against tick-borne diseases (TBDs). Moreover, we should also consider the movements of animals (as a result of migration/trade/games) having *F. tularensis* infection as a concerning risk of zoonoses. The European Centre for Disease Prevention and Control (ECDC 2019) advised to devise and

adopt the strategy of "One Health Initiative" or "One Medicine Perspective." This strategy should be based on the knowledge of the host, pathogen, tick disease triangle in relation with global warming, environmental changes, socioeconomic status of affected human societies, and the ecology of tick habitats and tick distributions. To break this triangle, an integrated tick control program is required throughout the disease-endemic regions. Recombinant anti-tick vaccines can be used as an advanced tick control technique especially in the case of animals. Another important approach is to promote disease-resistant animals instead of susceptible breeds and application of immunization programs.

According to the One Health concept, research projects for the control of TBDs should be a top priority area. On the other hand, the impact of climate change, urbanization, industrial, and agricultural pollution should be considered for their possible effect on infectious diseases. It is also suggested to implement a regional disease control program utilizing the One Health Concept to combat infectious diseases (ECDC 2019).

Conclusion

It is concluded that a major feature of tularemia is the variety of sources and modes of human infections acquired by handling or consumption of infected animal materials, vector bites, contact with aquatic environment, and inhalation of aerosols. The environmental conditions to which the bacterium has adapted may deviate greatly from that of another location and other environmental conditions. Thus, tularemia has been figuratively described as a chameleon with many faces that adapts to various environmental conditions. The climates of certain regions are suitable for tularemia infections in animals and humans. The presence of suitable tick habitats and prevalence of the pathogen make the environment favorable for the spread of this disease. Moreover, migratory birds are also a constant threat for the spread of new infections in some countries. Therefore, countries need their own disease management system for the control of infectious diseases. Awareness should also be given to the public to adopt precautionary measures for control of tularemia by One Health concept. Experts should design and implement advanced research projects for the control of tularemia through the development of safe, effective vaccines and anti-*Francisella* drugs should be a high-priority research area.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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