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Epidemiology of Tularemia

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Tularemia is considered to have existed in Anatolia for several thousand years. There are suspicions regarding its use in biological warfare in the Neshite-Arzawan conflict. The causative agent of tularemia may have first been used as a biological weapon in 1320-1318 BC. The disease has recently become a significant re-emerging disease globally as well as in Turkey. In the period of 2001-2010, Kosovo had the highest annual incidence in Europe at a rate of 5.2 per 100,000. Sweden, Finland, Slovakia, Czech Republic, Norway, Serbia-Montenegro, Hungary, Bulgaria, and Croatia follow with rates of 2.80, 1.19, 1.0, 0.81, 0.42, 0.4, 0.36, 0.21, and 0.15 per 100,000 people, respectively. Tularemia in Turkey was first reported in the soldiers living in the region very close to the Kaynarca Stream of Thrace in 1936. It has started to gain more and more importance, especially in recent decades in Turkey, due to a very high number of cases and its spread throughout the country. A total of 431 tularemia cases were recorded in Turkey in 2005, but a significant reduction was observed in the number of the cases in the next three years; the number of patients decreased to 71 in 2008. The number of cases increased again in 2009 and continued in subsequent years. The number of cases reached 428, 1531, 2151, and 607 in 2009, 2010, 2011, and 2012, respectively. The number of cases peaked in 2011 in Turkey, and was in fact higher than the total number of cases in all European Union countries. The number of cases is higher in females than males in Turkey. In Turkey, 52% of cases of tularemia diagnoses occur from December to March and the most common clinical presentation is the oropharyngeal form caused by contaminated water. Rodents are the most likely sources of tularemia outbreaks in Turkey as well as in Kosovo. Organisms such as ticks, flies and mosquitoes are vectors of tularemia transmission to mammals. Because ticks can carry the bacteria by both transovarial and transstadial transmission, they play a role in the life cycle of tularemia as both reservoir and vector.
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Key Words: Epidemiology, *Francisella tularensis*, tickborne disease, tularemia, water-borne disease

Also known as "rabbit fever", "hunters' disease", "deerfly fever", "tick fever", "O'Hara's Disease" and "Francis' Disease", tularemia is a common zoonotic disease in Turkey and throughout the world. The disease has started to gain more and more importance, especially in recent decades in Turkey due to a very high number of the cases and spread throughout the country (1, 2). Tularemia has recently become a significant re-emerging disease in the world because of the important role of bacteria in biological terrorism agents. Bioterrorism using anthrax has occurred in the United States, and an increase in tularemia cases has been the result of global warming, wars, natural disasters, human travel and animal movements (3-6). This review will focus on the epidemiological features of tularemia throughout the world and Turkey.

HISTORY

Tularemia was first been reported in Turkey in 1936, but it is considered to have existed in Anatolia for several thousand years (7-10). The presence of a disease, possibly tularemia, has been known in Central Anatolia since the 14th century BC, during the Hittite period. It is believed that this disease arrived by means of wars, travel, ticks or rodents to Anatolia from the Middle East region. Many people, including rulers and aristocrats, died from the disease in Syria, Egypt and Lebanon. It has led to social unrest, especially in Egypt (8-10). There are suspicions regarding the use of causative agent of tularemia as biological warfare in the Neshite-Arzawan conflict in 1320-1318 BC. It is thought that the Neshites may have won the conflict by sending diseased rams to the Arzawans, thereby weakening their military force. The source of the term "Hittite Plague" term may refer to this biological warfare event. There are many papyri belonging to this period in Hittite and Egyptian inscriptions (9, 10).

Tularemia is mainly reported worldwide in the northern hemisphere (2, 5). Many people have died from this disease in the Middle East, especially in the 1400s BC (10). Tularemia was first described as a disease of the rodent group called lemmings in the 16th century in Norway. It was also described in Japan and Russia in the 1800s (11, 12). The infectious agent was isolated by MacCoy and Chapin from dead ground squirrels in 1911 in Tulare, California, USA after the San Francisco earthquake in 1906. During this period, the bacteria had been referred to as *Bacterium tularense* to recognize the region

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of its discovery (5). The first human cases were reported by Lamb and Wherry in 1914 (12). Edward Francis was the first person who studied the epidemiology of the disease in humans, and described the clinical manifestations in humans. He stated that many people with different clinical presentations suffered from the same disease, and initially used the term “tularemia” for the disease. It was found to be transmitted through contact with the infected meat of rabbits and rodents. Serological tests were devised for the diagnosis, and a vector role of blood-sucking flies was established (11, 13, 14).

Bacterium tularense was initially included into the genera *Brucella* and *Pasteurella*, but was then designated as a new genus for its taxonomy in 1947. The genus, *Francisella*, was named in honor of Edward Francis, who contributed greatly to tularemia research. The species, *tularensis*, is named for Tulare County where tularemia was first observed. Another species, *F. philomiragia*, was placed in the genus *Yersinia* in 1959. Afterwards, it was included in the *Francisella* genus. This species is less virulent than *F. tularensis* (15). Another species, *F. noatunensis*, was isolated from Atlantic cod (*Gadus morhua* L.) as *F. philomiragia* subsp. *noatunensis* in 2007 (16, 17). It was later added to genus *Francisella* as a species of this genus (18). Recently, three additional species, i.e. *piscidida*, *hispaniensis*, and *guangzhouensis*, were also added to genus *Francisella* (19, 20). Therefore, six species are placed in the *Francisella* genus, including *F. tularensis*, *F. philomiragia, F. piscidida, F. noatunensis*, *F. hispaniensis* and *F. guangzhouensis* (21). Nowadays, *F. tularensis* is classified as four subspecies consisting of *F. tularensis* subsp. *tularensis* (Type A), *F. tularensis* subsp. *holarctica* (Type B), *F. tularensis* subsp. *mediasiatica, F. tularensis* subsp. *novicida* (5).

TRANSMISSION

Tularemia is more common in some groups of people. Groups at risk include foresters, hikers, hunters, people in contact with meat and animals, people living in rural areas, farmers, laboratory workers and veterinarians (2, 5, 22).

In humans, the clinical symptoms of tularemia may vary depending on the bacterium’s virulence, amount, mode of entry into the body, and the person’s immunity. Tularemia may be detected as only seropositive cases with no symptoms at all, or may lead to sepsis and death with quite different clinical findings (23-25). The rate of asymptomatic tularemia varies between 4-19% (14). So far, only one patient has died from tularemia in Turkey; this occurred in the Thrace region in 1936 (26).

The number of cases is higher (1.18 times) in females than males in Turkey (14). However, outside of Turkey, the number of cases is higher in males than females (27). The reason for higher female prevalence in Turkey may be due to the fact that women may be more active in household chores, and have more contact with contaminated water and with animal excrement or urine in food storage areas (14). Other reason for the different sex distribution may also be the fact that the oropharyngeal form of tularemia is more common in Turkey than in other countries; it is caused by the consumption of contaminated water or food. In contrast, the ulceroglandular form is the most common type of tularemia in other countries; it is caused by blood-sucking insects or arthropods (28). In the period of 2005-2009 in Turkey, 99% of 1091 cases were the oropharyngeal form of tularemia. According to the age of these cases, 19.3% of the patients were less than 20 years old. Most patients (53.8%) were in the age group of 30-64 years. This suggests that the disease usually affects adults. The average age is reported to be 38.7 years for women and 30.6 years for men (14).

The oropharyngeal form of tularemia is common in regions dominating aquatic cycle and is caused by the consumption of contaminated water or food. Urine, excrement or other excretions of animals involved in the aquatic cycle such as beaver, muskrat and voles can contain the causative agent and infect surface waters after rainfall in the winter months. The main reason for the oropharyngeal form is the consumption of contaminated water by people (28). In Turkey, 52% of tularemia diagnoses occur from December to March (Table 1) (29-49). Due to these reasons, the aquatic cycle appears to be the main ecological cycle for tularemia in Turkey. The emergence of tularemia cases (of 1441 patients, 91.5%) in Turkey usually starts in August and lasts until March.

Tularemia can exist in nature for long periods of time. It affects more than 100 mammals, birds, cold-blooded animals and arthropods (5). *F. tularensis* infects rabbits, mice, squirrels, beavers, rats, weasels, foxes, mink, sheep, cats, dogs, horses, pigs, many other wild mammals, more than 25 species of fowl, fish species, and many cold-blooded animals. Rodents (Rodentia; mice, rats, and squirrels) and hares (Lagomorphia) are the most important reservoirs for tularemia, according to epidemiological data obtained from various studies. Rodents are separated into two parts as terrestrial and aquatic rodents. However, all rodents are reservoirs in nature and take part in the life cycle of tularemia. Circulation continues among these animals in tularemia endemic areas. Although people and pets are not the main hosts, they are involved in these cycles as well. Throughout history, there have been noteworthy relationships between common animal deaths and outbreaks of tularemia in humans. A positive correlation is usually found in the relationship between the numbers of human cases and the numbers of animals infected with *F. tularensis* (39, 44, 50). High numbers of infected rodents such as mice, hares, and ground squirrels have resulted in an increase in the number of tularemia cases in humans in the Nordic countries and Russia (2, 5, 50).

The persistence of *F. tularensis* is considered to be divided into two cycles, i.e. the terrestrial and aquatic cycles (14, 22). Small rodents, hares, and arthropods (*Dermacento*r, *Amblyomma, Haemaphysalis* and *Ixodes spp.*) are very important in the terrestrial cycle of *F. tularensis*. Tularemia is usually fatal in these animals. The infectious dose of *F. tularensis* is very

TABLE 1. Monthly distribution of the tularemia cases in Turkey according to published literature

Regions	Years	Total number of the cases	Months												
			December	January	February	March	April	May	June	July	August	September	October	November	References
Kırklareli-Tekirdağ	1936	133							3	47	77	6			29
Bingöl-Tatvan-Reşadiye	1937	6									6				30
Kırklareli-Lüleburgaz	1945	15							2	5	7	1			31
Antalya-Bademağacı	1953	200									100	100			32
Bursa	1988-1998	205		Winter									Autumn		23
Ankara-Ayaş-Yağmurdede	1997	16	16												33
Düzce-Akçakoca	2000 and 2005	33			11		22								34
Bolu-Gerede-Yazıkara	2001	21										21			25
Amasya-Suluova	2004	86											86		35
Zonguldak-Kastamonu-Bartın		2004-2005	61		61										36
Kars-Sarıkamış	2004-2005	56			49							7			37
Kocaeli-Gölcük	2004-2005	145		145											38
Kocaeli-Karamürsel-Pazarköy	2005	17			17										39
Edirne-Lalapaşa-Demirköy	2005	10			10										24
Samsun-Havza	2005-2007	75	14	25	14	6	1				1		2	12	40
Sakarya-Kocadöngel	2005-2006	63			63										41
Bolu-Gerede-Nuhören	2006	6		6											42
Tokat	2005 and 2010	23	8					15							43, 44
Sivas	2008-2010	29	6	12	6	2								3	45
Çanakkale	2009	36	36												46
Çankırı-Çerkeş-Kadıözü	2009	18	16											2	47
Tekirdağ-Hayrabolu-Muzruplu	2010	8										8			28
Konya	2009-2010	40	21											19	48
Central Anatolia	2009-2011	139	23	23	38	29	10	1	3	3	7		2		49
Total number*	1936-2011	1441	210 (14.6)	176 (12.2)	249 (17.3)	115 (8)	32 (2.2)	22 (1.5)	13 (0.9)	55 (3.8)	198 (13.7)	177 (12.3)	124 (8.6)	70 (4.9)	

*Numbers belonging to more than one month were equally distributed to each of these months

low, i.e. 10^2 colony forming unit (CFU)/mL to 10^3 CFU/mL. The spleen of a mouse that died from tularemia contains 10^{10} CFU bacteria (51). Another study (52) showed that the bacteremic dose is greater than 10^8 CFU/mL in the blood and the lethal dose of bacteria is 10^9-10^{10} CFU/organ in the spleen, liver and lung of mice. However, some rodents can survive without clear symptoms of the disease. Bacteria can also be transferred to other rodents from asymptomatic rodents by blood-sucking arthropods such as ticks, flies, and mosquitoes, or they may persist in the environment.

Ticks are very important in the persistence of infection as they ensure the permanence of these bacteria in nature. Ticks infect the circulatory system of the host by their feces or bites. Bacteria are transmitted to wild animals or domestic animals (sheep, cattle, goats, horses, pigs, dogs, and cats) by ticks and blood-sucking flies (mechanical vectors). Some ticks can carry bacteria in their bodies for a lifetime (reservoir). Tick-borne tularemia infection in humans usually occurs in the summer months when ticks are more active. *F. tularensis* can survive up to two weeks in insects. Horse flies and deerflies in the United States and mosquitoes in Northern Eurasia are important in the transmission of the bacteria. In the natural cycle of *F. tularensis* subsp. *holarctica*, rodents associated with water (beavers, muskrats and other types of rats, ground and water voles, wild rabbits, squirrels and raccoons) play a major role as reservoirs (2, 14, 22, 50, 53).

The reservoir of *F. tularensis* varies from country to country. The most common reservoirs are *Arvicola terrestris* (water vole) and *Microtus arvalis* (field vole) as well as *Rattus rattus* (black rat) in Europe, *Arvicola terrestris*, *Mus musculus*, and hares in the *Lepus* genus in Russia, and hares in the *Sylvagus* genus in North America (50). In a study in Bulgaria, among 169 rodents caught in the wild, 37 of them were found to be infected with *F. tularensis* using molecular tests. Of these infected rodents, 32 and 5 were *Rattus rattus* and *Mus musculus*, respectively. *F. tularensis* could not be demonstrated in 9 *Apodemus agrarius* (54). However, two *A. agrarius* were shown to be infected by *F. tularensis* in a study of 64 rodents caught in Kosovo (55). When the carcass, meat, excrement, or urine of these animals contaminate food or water, tularemia results from the consumption of contaminated water or food. An increase in the rodent population such as voles is remarkable in epidemic periods of winter in Europe. It is not known exactly how hares interact with the microorganism, but it is thought that they are affected by the residues of mice on grasses and plants (50, 56).

There have been very few studies on the animals that carry tularemia in Turkey. Some authors (24) investigated the disease in sheep, cattle, mice, and rabbits during an outbreak that occurred in 2005 in the Thrace region (Edirne-Demirköy). They identified antibodies against *F. tularensis* at low titers ranging from 1/20 to 1/80 in one of 25 rabbits, in 19 of 27 cattle but in none of 19 sheep. *F. tularensis* was not isolated on the suspension of the three ticks on animals and none of the liver and spleen tissues of eight *Rattus rattus* and a dead rabbit in the village. The other authors (57) failed to find a causative agent by culture and molecular methods in the liver and spleen of 42 *Microtus socialis* collected from epidemic regions of central Anatolia.

Rodents are the animals suspected as the most likely sources of the tularemia outbreaks in Turkey and Kosovo in 1999 and 2000. A large number of water voles and other rodents were found dead in Lüleburgaz and Kırklareli in Turkey between the 1930 and 1945. In a survey conducted by Dr. Talat Vasfi Öz (26) in the region during this period, approximately 150 cases were diagnosed as tularemia in 28 villages and the district of Kırklareli as well as six villages in Tekirdağ. A strong relationship between mice and tularemia was obtained according to his observations. For example, Dr. Öz (26) described that when mice gnawed melons in a villager's house in Kırıkköy of Kırklareli, the household did not want to eat the melons for this reason. Nevertheless, the father ate the fruit and developed fever and swelling of his neck in a few days; he then suffered from the disease for several months. The stories of the villagers were interesting in terms of the important role between dead mice, contamination with their waste and tularemia. The villagers living in Hamzabey did not believe that their water was infected by the causative agent. A villager and his children drank water from the stream. After 2-3 days, they were seriously ill, their lymph nodes were swollen, and their body temperatures had increased (26). Rice cultivation, which needs a lot of water, was banned in the region following these observations, and it significantly reduced the number of rodents. Consequently, termination of the tularemia outbreak was achieved. After this period, an outbreak was seen in 1945 in Lüleburgaz, in the district of Kırklareli. Tularemia was eradicated, or at least was not diagnosed for a very long time after 1945 (5). It was observed that the number of mice remarkably increased in the year prior to outbreaks that occurred in 1998 (Bursa-Karacabey), in 2005 (Edirne-Demirköy), in 2010 (Kırşehir), and some other outbreaks (24, 57, 58). A relationship between tularemia in mice and human cases was suspected in Turkey, but this thesis could not be confirmed until recently (24, 57, 59). Recently, the causative agent of tularemia was found in mice collected from villages of the Thrace region where tularemia had been reported (60). In the mentioned study (60), its presence was demonstrated using molecular methods on two mice captured from Kaynarca village, which was considered to be the main focus of the outbreak in 1936. Thus, it was shown that the causative agent of tularemia was carried by voles and their potential role in tularemia transmission was confirmed in Turkey for the first time (60).

F. tularensis is highly resistant to external environmental conditions. Especially amoebae living in water (*Acanthamoeba Castellani*) are important for the bacteria that survive in nature (50, 61). Bacteria can survive for years in water, soil, mud, swamps, animal wastes, barns, and frozen meats (6, 11, 12, 14).

Humans are one host for *F. tularensis*, as well as many species of birds, fish and reptiles (2, 62). Although some data are missing in birds, it is thought that they play a role in the spread of the agent worldwide (63, 64). Birds, rodents, and hares can carry the same ticks in some regions. For this reason, they are thought to contribute to the persistence of *F. tularensis* in nature (50).

Organisms such as ticks, flies and mosquitoes are responsible for the transmission of tularemia to mammals. This transmission is possible among wild animals, pets, and humans. Because ticks can carry the bacteria by both of transovarial and transstadial transmission, they play a role in the cycle of tularemia as both a reservoir and a vector. While *Ixodes ricinus* and *Dermacentor reticularis* ticks are the main sources of tularemia in Europe, and they play a central role in most regions of America, flies are more common vectors in other regions. *Amblyoma*, *Dermocentor*, and *Ixodes species* are responsible for transmission. *Crysops* (deer flies), which belong to the family *Tabanidae*, and *Tabanus* (horse flies) can mechanically infect animals with their mouth organs. These flies carry *F. tularensis* in the western United States and Russia, and most of the tabanid flies can be infected with *F. tularensis* (65). Transmission is also possible by *Aedes*, *Culex* or *Anopheles* mosquitoes and *Ixodes*, *Dermocentor* or *Rhipicephalus* ticks (50). Most of the cases in the Nordic countries are caused by the bite of mosquitoes. Mosquito-transmitted tularemia cases are more often diagnosed during the summer months, unlike water-borne tularemia. Some mosquitoes are infected in the natural environment, but they carry only the mechanically causative agent because there are no bacteria in their salivary glands. *Aedes cinereus* mosquitoes are a naturally infected form, first reported in Sweden (66). Edward Francis reported that *Cimex lectularis* (bedbugs) is important for tularemia transmission. In subsequent years, it was seen that bedbugs could play a role in the transmission of tularemia in most cases as a vector. Water-borne oropharyngeal tularemia is a common form, and tick-borne tularemia is rarely reported in Turkey. Two tularemia cases were reported in Yozgat in 2011 after tick bites (67). There was also a suspicion of tick exposure in three cases reported in Düzce in 2000 (68). Transmission by mosquitos or other flies has not been accurately described in Turkey. However, it is thought that some soldiers could have been infected by insects at the Lüleburgaz Military Facility during the Kaynarca outbreak that occurred in 1936 (26).

Miller (69) was the first researcher to describe water-borne tularemia. Dr. Tahsin Berkin and Dr. Talat Vasfi Öz (26) concluded that tularemia was mostly a water-borne disease in the Thrace outbreaks between 1936 and 1937. It was thought that the Kaynarca River, with a military garrison nearby, was the main source of the disease. This thesis was supported by the anamnesis of the soldiers who had bathed in the stream and then had suffered from the disease, as well as the existence of the disease in the villages near the stream and among rice field workers and some villagers that had bathed in the stream. Unfortunately, studies on both water samples and samples of animals such as rabbits and ticks collected from the local environment failed to confirm the contamination. Therefore, how animals contaminated the water and which animals were contaminated with bacteria was not exactly demonstrated (26, 29).

REPORTED TULAREMIA CASES AND FREQUENCY

Tularemia has been reported in many regions of the world since its original description in the United States. There have been many tularemia cases in parts of North America, central Asia, Russia, the Nordic countries, the Balkans, and Japan (1, 22). Especially North America and the Nordic countries are endemic areas for tularemia. Outbreaks also occur in Eastern Europe and Russia. The incidence of tularemia is 0.5 to 5/one million cases per year in the United States. A major outbreak occurred in 1939 that affected 2,291 people in the United States. While the annual number of cases was about 900 in the United States in 1950, it gradually decreased in subsequent years, and the number of the cases was approximately 100 patients in 2010 (70, 71). A tularemia outbreak affected more than 100,000 people in the Soviet Union in 1940 (70). In 1950, a large outbreak occurred in Germany and a large number of cases were reported in countries such as the Czech Republic, France, Sweden and Finland. The prevalence of tularemia increased after the Second World War, especially in Eastern European countries and Russia. The rise in the number of the cases was especially remarkable in the Balkan countries in recent decades compared with the incidence of tularemia throughout the world (14, 22, 70, 71). Outbreaks occurred in 1999-2000 because of the negative effects of the war in Kosovo. In the following years, the outbreak continued there, and the number of cases reached 1,221 between 1999 and 2010. In the period 2001-2010, Kosovo had the highest annual incidence of tularemia in Europe at a rate of 5.2 per 100,000 (71). Sweden, Finland, Slovakia, Czech Republic, Norway, Serbia-Montenegro, Hungary, Bulgaria, and Croatia followed with rates of 2.80, 1.19, 1.0, 0.81, 0.42, 0.4, 0.36, 0.21, and 0.15 per 100,000 people, respectively (72). Interestingly, tularemia has not been reported in the United Kingdom, Iceland, Africa, South America and Antarctica. To date, Australia has had only two tularemia cases related to *F. tularensis* (73, 74).

Tularemia in Turkey was first reported in soldiers living in the region very close to the Kaynarca stream in Thrace in 1936. The majority of these cases were soldiers who had a history of bathing in the Kaynarca stream and were admitted to the Lüleburgaz Military Hospital. Another small group included the villagers living in the same region and using the same water source (7, 29). A second tularemia outbreak was occurred in Lüleburgaz nine years later (31). These outbreaks affected 168 people in total (26). Additionally, some cases were reported in several places in Turkey (some parts of eastern Anatolia, Tatvan, and Konya). Six patients were affected in the Tatvan-Reşadiye outbreak (30).

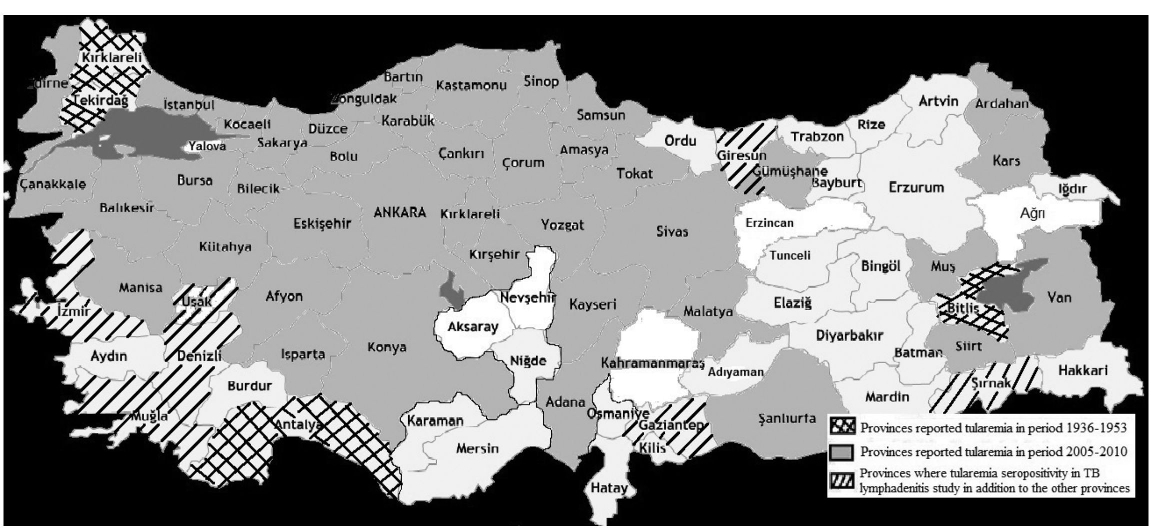

FIG. 1. Distribution of tularemia in the cities of Turkey (72)

In 1953, Turkey's biggest tularemia outbreak was reported. According to the researcher Ibrahim Ethem Utku, about 300 (at least 200) people or 154 patients (according to hospital records) suffered from the outbreak which occurred in Bademağacı village, 57 km north of Antalya (32).

Tularemia had a quiet period between 1953 and 1988 in Turkey. Then, it emerged in new outbreaks in many villages of Bursa-Karacabey in 1988 (58). In the research performed on this outbreak, an increase in the number of mice was observed in the villages at the time of the epidemic period, and water was suspected as the source of the outbreak (75). Sporadic cases or small outbreaks continue to be reported from Bursa to date (23). A total 372 patients were diagnosed with tularemia in the Bursa region between 1988 and 2004. Another outbreak affecting 70 people was also reported in Bursa, i.e. in Yörükali village, in 2005 (76, 77).

Tularemia outbreak reports have increased in recent decades in Turkey. These reports are as follows: 16 cases in Ankara Ayaş Yağmurdede (1997); 35 cases in Bilecik Pazarcık Ahmetler (1998); 49 cases in Samsun (1999 and 2001); 40 cases in Sinop (2000); 22 cases in Yalova (2000); 33 cases in Düzce (2000 and 2005); 30 cases in Bolu Gerede (2001-2006); 126 cases in Balıkesir (2002); 129 cases in Amasya Suluova (2004); 61 cases in Zonguldak, Kastamonu and Bartın of Western Black Sea Region (2004-2005); 56 cases in Kars (2004-2005); 162 cases in Kocaeli (2004-2005); 10 cases in Edirne Lalapaşa Demirköy (2005); 75 cases in Samsun-Havza (2005-2007); 63 cases in Sakarya (2005 and 2006); 23 cases in Tokat (2005 and 2010); 20 cases in Çankırı Çerkeş Kadıözü (2009); 36 cases in Çanakkale (2009); 29 cases in Sivas (2009-2010); 8 cases in Tekirdağ Hayrabolu Muzruplu (2010) and 40 cases in Konya (2010) (14, 24, 25, 28, 33-37, 40, 42-46, 48, 49, 78).

After the period when outbreaks were reported all over the country in 2009, cases (more than 500) were mostly reported from the central Anatolia region, especially from Yozgat (49). If it was considered that the disease in some patients was misdiagnosed and not included in the statistics, the number of the cases would be much higher in Turkey. In fact, very interesting results were obtained in a comprehensive study on tuberculosis which was confused with tularemia. In this study, the sera of the patients with a diagnosis of tuberculous lymphadenitis in the Tuberculosis Dispensaries of Turkey were investigated for tularemia antibodies. It was shown that a significant proportion of these cases could be tularemia. Seropositivity was found even in areas never having reported tularemia (Figure 1) (79).

Because reliable data cannot be obtained about tularemia, it was included in the list of "The Notification System of Communicable Diseases (Group C)" by the Turkish Health Ministry in 2005 (5, 14). In this way, more reliable epidemiological data were obtained after 2005. A total of 431 tularemia cases in Turkey were noted in 2005, and a significant reduction was observed in the number of the cases in the next three years, as the number of patients decreased to 71 in 2008. The number of cases again increased in 2009 and continued in the following years. The number of cases was 428, 1531, 2151, and 607 in 2009, 2010, 2011, and 2012 respectively (14, 72, 80). The number of the cases peaked in 2011 in Turkey, and was higher than the total number of cases in all European Union countries (Figure 2).

In recent years, increasing causes of tularemia worldwide have been climate change, wars, natural disasters, human travels and animal movements. Global warming has resulted in an increase in the average temperature during the year, which has given rise to a very important change in the cycle of tularemia. In a study performed in Sweden, a climate scenario was developed using computer software in order to understand what could happen with tularemia in the case of global warming. In this study, an annual average 2°C temperature increase was predicted from 2010 to 2100. The results of this study indicated that global warming would lead to an increase in tularemia cases in coming decades (81).

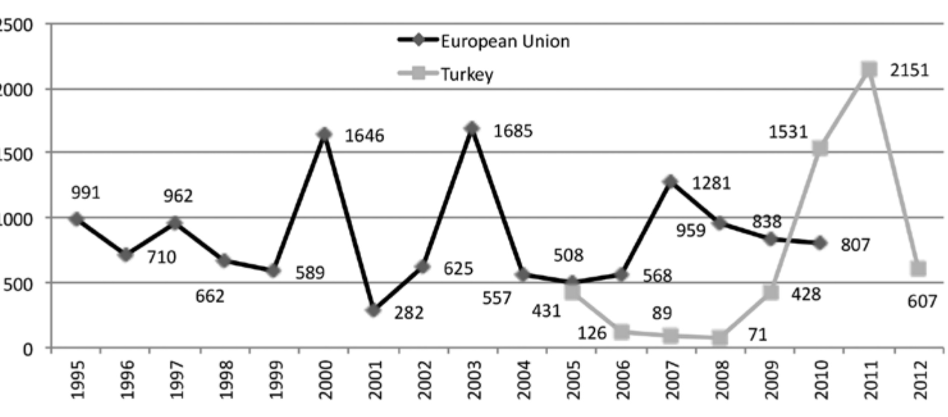

FIG. 2. Comparison of the number of the tularemia cases in European Union countries and Turkey

CONCLUSION

Avoiding contact with vectors and reservoirs plays an important role in the control of this disease because tularemia is a zoonotic disease. Factors such as global warming, the migration of birds, and ticks on these birds cannot be controlled, but human contact with these vectors and reservoirs can be avoided. In rural areas, using protective clothes and repellents, as well as avoiding of contact with dead animals and wild animals provide protection from the disease. Hygienic conditions for food and beverages are more important than other measures in the control of the disease, especially in countries such as Turkey where the oropharyngeal form is more common. The consumption of chlorinated water and well-done meat and animal products prevents contamination via the digestive system. Early diagnosis of the disease effects both the treatment and the measures to be taken to control the disease. Performing vector surveys and investigations into the hygienic control of water resources in endemic or high risk areas will help predict probable outbreaks such that the necessary measures can be taken before the disease outbreak occurs.

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