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# Tularemia outbreaks in Kayseri, Turkey: An evaluation of the effect of climate change and climate variability on tularemia outbreaks☆

Elcin Balci[a], Arda Borlu[b], A. Ulu Kilic[c], Hayati Demiraslan[c], Ahmet Oksuzkaya[b], Mehmet Doganay[c,*]

[a] *Department of Public Health, Faculty of Medicine, Erciyes University, Kayseri, Turkey*
[b] *Provincial Directorate of Health, Kayseri, Turkey*
[c] *Department of Infectious Diseases, Faculty of Medicine, Erciyes University, Kayseri, Turkey*

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**Summary**
*Objectives:* The aim of this study was to evaluate the epidemiological characteristics of tularemia outbreak and the effect of climate variability on this outbreak in Kayseri.
*Methods:* The outbreak places, infection dates, source of infection, and the number of cases were recorded and analyzed. This information was obtained from the Regional Public Health Department. Climate data were supplied by the Regional Meteorological Service.
*Results:* The first case in Sariz was recorded in 2005. Thereafter, 2 cases were reported in 2006 and 1 case in 2007. During 2010, 21 cases were recorded in 7 towns, 62 cases in 2011 and 27 cases in 2012. A total number of 110 cases were recorded in 12 out of 16 towns in Kayseri Province between 2010 and 2012. The majority of cases were seen in the north-eastern, east and south-eastern parts of Kayseri Province; located in higher altitudes (over 1000 m from sea level). It was accepted that the outbreak was originated from water sources and was confirmed by few number of water samples collected from outbreak areas. Considering climate variations, the outbreak occurred between 1988 and 2009 during a dry, low humid, high temperature period after rainy season.

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* Corresponding author at: Department of Infectious Diseases, Faculty of Medicine, Erciyes University, 38039 Kayseri, Turkey. Tel.: +90 352 2076666x22055; fax: +90 352 4375273; mobile: +90 533 3682042.
*E-mail addresses:* drelcin71@gmail.com (E. Balci), ardaborlu@gmail.com (A. Borlu), draysegululu@yahoo.co.uk (A.U. Kilic), tigin68@hotmail.com (H. Demiraslan), droksuzkaya@gmail.com (A. Oksuzkaya), mdoganay@erciyes.edu.tr (M. Doganay).

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*Conclusion:* A tularemia outbreak was observed between 2010 and 2012 with the initiation of rainy years. High temperature for a long period accompanied by low rainfall and low humidity may affect the vector's biology and initiate a tularemia outbreak in high plateaus in Kayseri Province and around.


## Introduction

Tularemia is a zoonotic infection, and it is often a vector- or water-borne disease. The etiological agent of tularemia is *Francisella tularensis*, which primarily causes disease in wild lagomorphs and rodents. These animals are also natural reservoirs for this bacterium. Human infections are often the result of handling infected animal carcasses, consuming undercooked, infected rabbit meat, or being bitten by ixoid ticks or tabanids. Infection can also be caused by the contamination of the skin and mucous membranes, such as the nose, eyes, or mouth, with contaminated fluids from infected animals or contaminated water, or by the inhalation of dust particles [1—3]. In Europe and Turkey, *F. tularensis* subsp. *holarctica* (Type B) has been associated with outbreaks, and human outbreaks have originated from contaminated water sources, such as rivers and lakes [3—5]. A wide range of arthropods have been shown to transmit tularemia to mammals, including ticks, tabanid flies (horseflies and deerflies), fleas, and mosquitoes. Ecological and climate changes may have important effects on wild lagomorph, rodent, and vector populations [1,2,6]. Human infection often occurs in geographically localized outbreaks. Currently, tularemia is observed in the Northern hemisphere and is considered an epidemic disease in some parts of Turkey [1,2,4].

Climate changes and zoonotic diseases are new global issues in medicine. Climate change is attributed directly or indirectly to human activities due to the alteration of the composition of the global atmosphere. Zoonotic vector-borne diseases are increasing health problems because climate variability affects vector biology and disease transmission. The population and behaviors of wild lagomorphs and rodents are also affected by climate variability. Climate variability and tularemia were recently evaluated in Sweden and the Russian Arctic [6,7], but the effect of climate change on tularemia has not yet been investigated in Turkey.

The latest tularemia outbreak in Turkey was reported around Bursa in the Marmara Region in 1988. Thereafter, the infection spread to the Turkish Thrace Region and Central Anatolia [4,8]. The first case in this region was recorded in 2005, and the current outbreak began in 2010 in Kayseri, which is located in Central Anatolia. This was the first outbreak of tularemia in Kayseri in the last century. The aim of this study was to evaluate the epidemiological characteristics of this outbreak and the effect of climate variability on the tularemia outbreak in Kayseri.

## Materials and methods

### Data on human tularemia

This is a cross-sectional study evaluating the relationship between climate variability and tularemia in Kayseri Province. Kayseri, which has a population of 1 274 968, is located in Central Anatolia and has one university hospital and a referral tertiary care hospital. There are also many private outpatient clinics and secondary care hospitals. Human tularemia is a notifiable disease in Turkey; i.e., when a physician diagnoses tularemia, the case must be reported to the Health Office. The documentation for the tularemia cases was obtained from the Regional Public Health Department in Kayseri. This study only included tularemia cases in Kayseri province; cases from other locations were excluded. The tularemia notification forms for the confirmed tularemia cases were reviewed by the authors. The patient's gender, age, residence, infection date, source of infection, and the number of cases were recorded and analyzed. This study was approved by the Research Ethics Committee of Erciyes University.

### Tularemia case definition

Confirmed tularemia cases were defined as patients with compatible clinical findings and positive serological titers $\geq$160 as determined by the microagglutination test (MAT) or a seroconversion with a 4-fold increase in antibody titers between 2 serum samples collected at least 2 weeks apart. An outbreak of tularemia was defined as an increase in the number of reported cases that were expected on the basis of previous reports during non-epidemic periods.

**Table 1** Population, altitude, and tularemia cases in the towns of Kayseri Province.

| Town | Altitude (m) | Year | | | Total cases | Population | Incidence rate (per 100 000) |
|---|---|---|---|---|---|---|---|
| | | 2010 | 2011 | 2012 | | | |
| Pınarbaşı[a] | 1500 | 9 | 3 | 1 | 13 | 27 045 | 48.06 |
| Sarız[a] | 1500 | 2 | 3 | 2 | 7 | 10 720 | 65.29 |
| Tomarza[a] | 1397 | 0 | 9 | 5 | 14 | 25 496 | 54.91 |
| Bünyan | 1375 | 0 | 0 | 4 | 4 | 29 955 | 13.35 |
| Akkışla | 1350 | 1 | 3 | 0 | 4 | 6 621 | 60.41 |
| Hacılar | 1350 | 0 | 0 | 0 | 0 | 12 381 | 0 |
| Felahiye | 1340 | 0 | 2 | 5 | 7 | 6 512 | 107.49 |
| Sarıoğlan | 1330 | 2 | 12 | 0 | 14 | 15 324 | 91.35 |
| Özvatan | 1292 | 3 | 9 | 5 | 17 | 3 980 | 427.13 |
| Develi[a] | 1180 | 3 | 5 | 1 | 9 | 64 381 | 13.97 |
| Yeşilhisar | 1150 | 0 | 0 | 0 | 0 | 16 324 | 0 |
| Talas | 1100 | 0 | 0 | 0 | 0 | 113 372 | 0 |
| Melikgazi[a,b] | 1054 | 1 | 8 | 1 | 10 | 509 309 | 1.963 |
| Kocasinan[a,b] | 1054 | 0 | 7 | 3 | 10 | 372 507 | 2.684 |
| İncesu | 983 | 0 | 0 | 0 | 0 | 24 127 | 0 |
| Yahyalı | 590 | 0 | 1 | 0 | 1 | 36 914 | 2.708 |
| TOTAL | | 21 | 62 | 27 | 110 | 1 274 968 | 8.627 |

[a] Meteorological stations.
[b] Kayseri central city towns.

## Patients, clinical samples, and diagnosis

A patient with suspected tularemia in the Kayseri province is generally referred to the Department of Infectious Diseases of the State Hospital or Erciyes University Hospital for further investigation. After confirmation of the diagnosis, patients are transferred to infectious disease clinics. All clinical samples obtained from the suspected patients are sent to the Regional Health Department in Kayseri.

Outbreak regions were investigated by public health physicians, and environmental samples were obtained. For preventive measures, family or public health physicians also provided information about the disease to people living in the at-risk areas.

All samples were transported to the Zoonotic Diseases Department at the National Public Health Laboratory (NPHL) in Ankara by the Regional Health Office. The NPHL has been authorized as a reference laboratory for the diagnosis of tularemia by the Turkish Ministry of Health. MAT, polymerase chain reaction (PCR), and indirect immunofluorescence assays were performed as diagnostic tests.

## Climate change data

Meteorological data were obtained from the Kayseri Regional Meteorological Service and the website of the Turkish State Meteorological Service [9]. Daily observations of humidity, rainfall, and temperature were recorded at 5 meteorological stations in the Kayseri Province: Kayseri center, Pinarbasi, Tomarza, Sariz, and Develi. These stations calculated the monthly minimum and maximum temperatures (°C), rainfall (mm), and relative humidity (%). In addition, the annual average temperature, total rainfall, and relative humidity were obtained for each town. The altitude and population density of the towns were also recorded. The temperature, humidity, climate variability, and rainfall charts were reviewed and recorded.

### Data analysis

Data analysis was performed using Microsoft Excel. The number and distribution of tularemia cases in Kayseri Province, the geographical characteristics of the outbreak region, the annual rainfall, the humidity and temperature changes, and the altitude and climate variability were analyzed.

# Results

## Epidemiological data

The first case of tularemia was recorded in 2005 in Sariz in Kayseri Province. Thereafter, 2 cases were reported in 2006 and 1 case in 2007. There were no cases between 2007 and 2009, which was followed by an outbreak in 2010. The majority of the cases

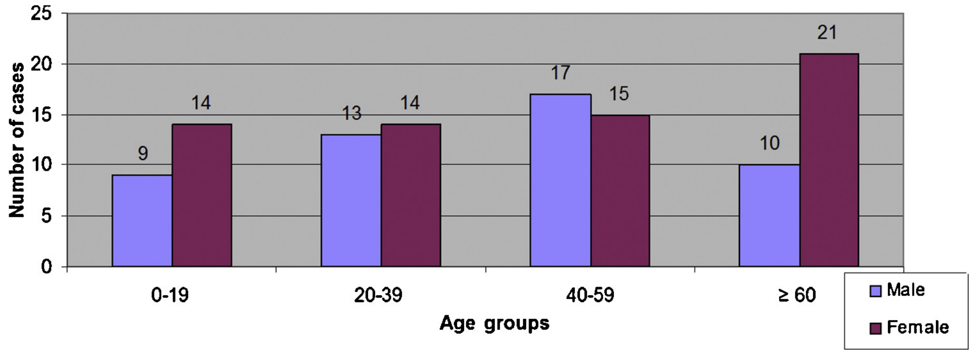


**Figure 1** Distribution of cases according to age group.

in this outbreak (62 of 110) were recorded in 2011. A total of 110 cases were recorded between 2010 and 2012. Of these cases, 91 patients were living in the village or remained in the center of the city or town.

Table 1 summarizes the tularemia cases according to year and region. The overall incidence rate of the disease was 8.627 per 100 000 people. A total of 49 male and 64 females (age range, 1—86 years) contracted the disease. The tularemia cases were distributed among all age groups, with the highest incidence among middle-aged groups. There were 23 patients aged 0—19 years, 27 aged 20—39 years, 32 aged 40—49 years, and 31 patients aged over 60 years (mean: 43.15; median: 47.00 ± 22.37; min: 1; max: 86 years old) (Fig. 1).

## Geographical characteristics and climate variability

Kayseri Province is located in the center of Anatolia, between 35° E and 30° E longitude and 38° N and 43° N latitude. The population was approximately 1 274 968 at the end of 2012. There are 16 towns, with altitudes ranging from 590 to 1500 m above sea level. Two rivers cross the Kayseri Province, including the Kizilirmak River, which crosses 25 km northwest of Kayseri City. There are two dams in the province; the Yemliha dam was constructed in 2003 across the Yemliha River, which is 70 km long and has a catchment area of 85.30 $km^2$. The Sarioglan dam was constructed on the Kizilirmak River in 2002 and has a catchment area of 2.65 $km^2$. The Zamanti River also runs through the southeastern part of the Kayseri province, originating from Pinarbasi and emptying into the Mediterranean Sea. A non-active volcanic mountain (Erciyes Mountain) with an elevation of 3998 m is located between Kayseri City and Develi. Kayseri Province is also surrounded by the Taurus Mountains to the south. There is a wetland plain covering 39 000 ha with an altitude of 1079 m between Develi, Yesilhisar, and Inscesu in the southwestern part of Kayseri Province.

Fig. 2 shows the monthly distribution of the cases recorded in Kayseri Province. The majority of the cases (94 of 110 cases, 85.45%) were recorded between December and April.

The patients' locations are indicated on the Kayseri map, and Fig. 3 shows the geographical distribution of the cases. A majority of the cases (59.0%; 65 of 110) originated from 5 towns (Pinarbasi, Sariz, Tomarza, Sarioglan, and Ozvatan) located in the north and northeastern parts of Kayseri Province. The altitudes of the towns in which tularemia cases were reported are all greater than 1054 m above sea level.

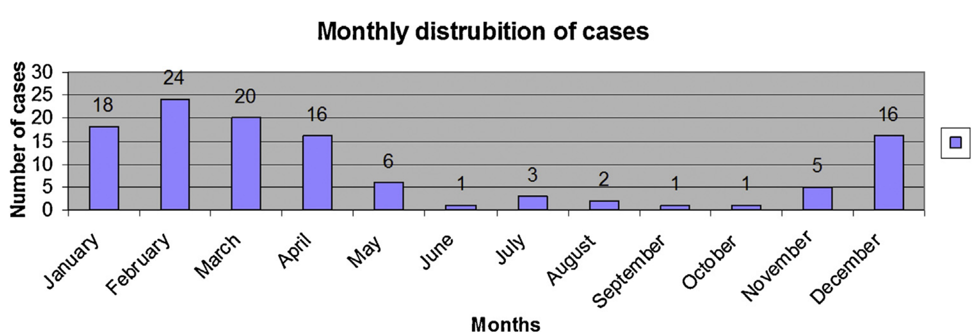


**Figure 2** Monthly distribution of cases in Kayseri Province.

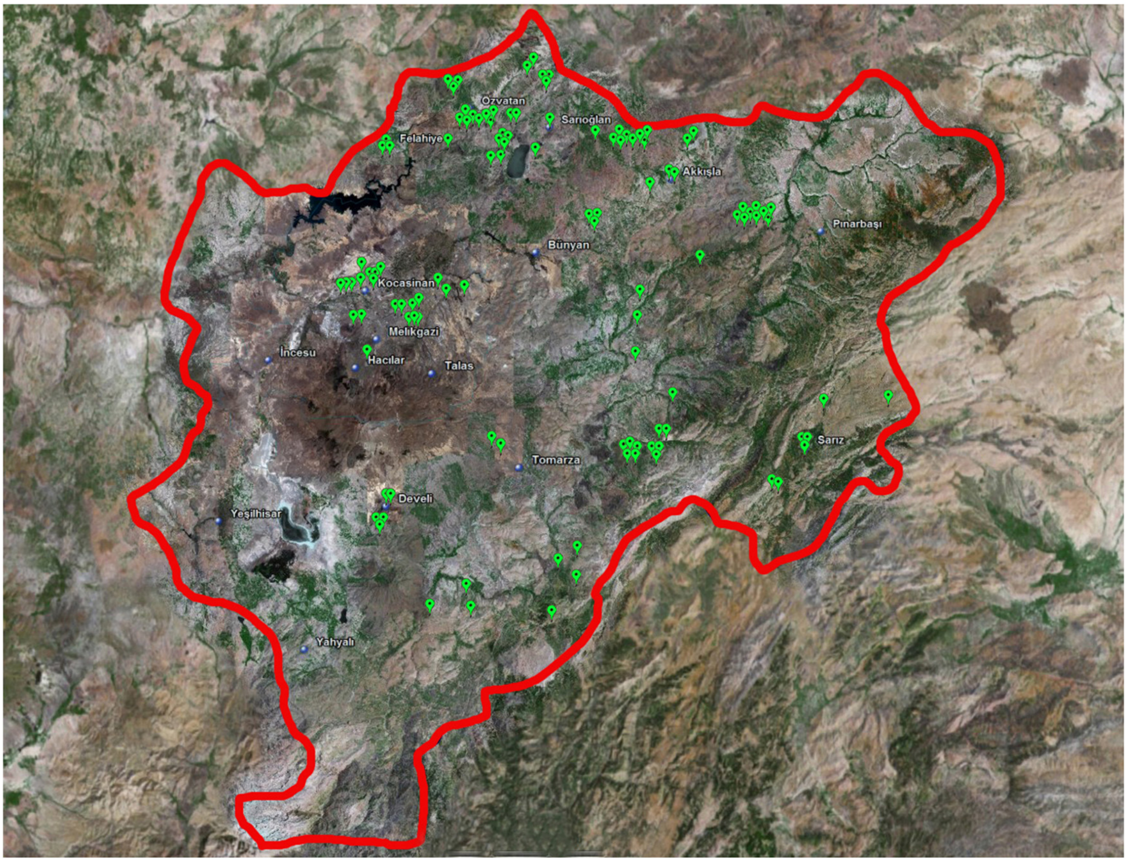


**Figure 3** Distribution of tularemia cases recorded during the 2010—2012 outbreak in Kayseri.

**Central towns in Kayseri**

Two towns in Kayseri, Melikgazi and Kocasinan, have many villages. All of the cases recorded in these central towns came from the surrounding rural areas. In this region, high temperatures were observed during 1994—1998, 2001—2003, and 2008—2010, and rainfall and humidity were significantly decreased during 1994—2009. Rainfall was reported to be over the annual average amount in 2010 and 2011 in the outbreak areas.

*Pinarbasi*: The town of Pinarbasi is located on a high plateau (altitude: 1500 m) and has a population of 27 045. The Zamanti River originates from the northeastern side of the town and flows through to the southwestern side of Pinarbasi. Pinarbasi experienced warm periods in 1994—2002 and 2005—2010 before the outbreak. Rainfall was estimated to be less than the average amount in 1999—2007. The humidity was also lower in 1993—2010. During the outbreak, 13 cases were recorded, and of these, 9 cases came from the village of Kaynar.

*Sariz*: The population of this town is 10 720, and it has an altitude of 1500 m. A total of 7 cases were recorded, of which 4 were reported from various villages around Sariz. There was no serious temperature variation in 1990—2011, except during 2001 and 2010. The annual average temperature was 2 °C above the mean temperature. Small amounts of rainfall were recorded during the periods 1982—1987, 1992—1994, and 1998—2004. Lower humidity was also recorded during 1998—2007.

*Tomarza*: Tomarza has a population of 25 496 and an altitude of 1397 m. A total of 14 tularemia cases were recorded in this town. All of the cases were reported from villages around Tomarza (5 in Tatar village, 2 in Avsarobası village). High temperatures were recorded in Tomarza in 1994—2007. Significant decreases in rainfall were recorded in 1992—1995, 1998—2001, and 2008—2010. There was a substantial decrease in humidity after 2007.

*Develi*: The population of Develi is 64 381 and the town has an altitude of 1180 m. A total of 9 cases were recorded in Develi during the outbreak, and all cases originated from the rural areas near this town. A substantial increase in temperature was observed in 1994—2010, and decreased rainfall was recorded with low humidity during this same period. Develi experienced dry years in 1992—1997 and 1999—2008. In 2009 and 2010, Develi experienced heavy rainfall over the average level, but rainfall returned to below average in 2011.

### Infection control studies

Environmental and water samples were collected from endemic areas. Water samples (500—1000 mL from each site) were obtained from drinking and other water sources, including street taps from several points. Homes, outbuildings, spring waters, and other water sources were examined for evidence of contamination by rodent carcasses or excrement. Fecal specimens were collected from captured animals and from food storage areas (cellars). Water samples were positive for *F. tularensis holarctica* in the village of Avsarobasi in the town of Tomarza and in the town of Ozvatan in 2011, as well as in the village of Avsarobasi in the town of Tomarza, the village of Guzelce, and the town of Ozvatan in 2012.

The outbreak area and the families living there were visited by family or public health physicians. For the purposes of public information and awareness, the affected families and people living in risky areas were trained about transmission and how to control the infection. They were instructed to boil water that was unchlorinated or of unknown source, use gloves when handling, skinning, or dissecting wild animals, avoid the consumption of raw meat, and wash vegetables and fruits thoroughly before consumption. To combat the outbreak, regular water chlorination procedures were performed by the authorities in the towns and villages.

The questionnaire and education program for physicians were initiated by the authors (EB, AB, MD) on April 6—8, 2011 to evaluate physician knowledge of tularemia. The questionnaire comprised a set of questions about the transmission and clinical symptoms of tularemia and the management and prevention of the disease. An infection control education program was then organized for 501 physicians that provided clinical information on the spread of the disease and the clinical forms, diagnosis, and treatment of tularemia. Of the 501 physicians, 368 were family physicians, whereas 113 were specialists working in government or private hospitals, and 20 were physicians working in public health centers.

## Discussion

The first tularemia outbreak in this century was recorded in 1936 in Luleburaz in the Thrace region of Turkey. A major outbreak was reported in 1953 in Antalya, which is located on the Mediterranean Coast. In 1988, another outbreak that resulted in 64 cases was recorded in the Bursa province of the Marmara region. In 2005, other outbreaks were reported along the Kelkit Valley in central Anatolia and nearby areas. A total of 4824 cases were recorded between 2005 and 2011 in all of Turkey. Many experts suggested that the outbreaks in Turkey generally originated from water sources, and infection was observed only in rural areas, particularly among farming families, including in housewives, children, hunters, and forest workers [1,3,4,8,10,11]. The first case in Kayseri Province was recorded in 2005. Although only a few water samples tested positive for *F. tularensis* by PCR, drinking contaminated water was the major source of the outbreak in Kayseri Province. Accordingly, almost all cases were the oropharyngeal or glandular forms of the disease.

Global warming has accelerated in recent years, mainly due to greenhouse gas emissions caused by human activity. The world has warmed by approximately 0.75 °C in the last 100 years. The rate of increase in the last 25 years, however, is much higher, at over 0.18 °C per decade. This temperature increase is widespread over the globe, and land regions are warming faster than the oceans [12].

Meteorological data from Kayseri Province shows increased temperatures and decreased rainfall in the last 20 years. Although the top of Erciyes Mountain has always been covered with thick ice during summer time, in the last decade, the ice has melted and disappeared during the summer season. This is an important indicator of the warming of the Kayseri province. Kayseri experienced a dry period between 1992 and 2009. The tularemia outbreak was observed at the start of the rainy seasons during 2010—2012. Moreover, the tularemia cases were recorded on high plateaus, at altitudes above 1050 m above sea level. The cases were also clustered between December and April.

A sudden increase in the population of *Simulium* flies was observed in the basin of the Kizilirmak River and nearby areas following the release of water from the Yemliha Dam for the production of electricity in 2006 and 2007. The role of this species in the transmission of tularemia is not yet known, but this fly might have a potential role in transmission in endemic area [13].

Another important ecological change was an increase in the field mice population in Kayseri Province. A control study was conducted by The Plant Protection Research Institute of Ankara between 2007 and 2012 to evaluate the harmful effects of these mice on cereal plants in Kayseri.

Although field mice play important roles in the transmission of tularemia, no study has yet been performed on field mice in Kayseri to determine their role in the transmission of tularemia [13].

Infection can be acquired by humans through different means, and the clinical presentation of disease varies according to the predominant mode of contamination. The oropharyngeal form arises after ingestion of contaminated water or food, whereas the ulceroglandular and glandular forms occur via arthropod bites (ticks, mosquitoes, tabanids) [1,3,8,10,11]. The clinical presentation of tularemia alters from one geographical area to another according to the mode of transmission. Changing temperature and rainfall influences the transmission and geographical distribution of the disease. Animal host populations and vectors are particularly sensitive to these climate factors [5]. Global warming has been implicated as a determining factor in vector-borne infections. The increased incidence of the tick population in Europe has been attributed to the warmer climate. Though ticks can live in warm, dry climates, mosquitoes require humid conditions [14]. High incidences of mosquitoes have been correlated with the number of human tularemia cases in Sweden [6]. In Turkey and, to a lesser extent, Russia and the Balkans, the dominant mode of transmission is the consumption of contaminated spring water. Increases in the rodent population and the subsequent mass death of these animals has been reported preceding human tularemia outbreaks [15]. The number of tularemia cases in humans was significantly correlated with the seroprevalence of *F. tularensis* in European brown hares and the population density of common voles in Hungary [16]. These animals serve as disease reservoirs. High rainfall is an environmental factor that affects the abundance of rodent populations and outbreaks of rodent-borne diseases. Poor sanitary conditions have been implicated in tularemia outbreaks, particularly in rural areas.

The Crimean-Congo hemorrhagic fever (CCHF) virus has a similar geographic distribution in Anatolia and is particularly endemic in the Kelkit Valley, but the number of cases reported in Kayseri has decreased since 2003 [17]. While CCHF is a tick-borne disease, the peak number of cases correlated with the hot and dry climate period in Kayseri [18].

Kayseri has experienced a long period of dry years. The tularemia outbreak occurred upon the initiation of a rainy period within the normal range. By the end of 2012, the incidence of tularemia again receded. This study describes the first outbreak of tularemia in Kayseri Province and determines the association between climate change and the reemergence of tularemia in a restricted endemic area. However, this study was a cross-sectional study with a small number of cases living in a restricted area, which is a noteworthy limitation. Future studies are needed to determine the association between tularemia, ecological changes, vector biology, and climate variability.

## Conflict of interest statement

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*Competing interests*: None declared.
*Ethical approval*: Not required.

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