EPIDEMIOLOGY

RETROSPECTIVE ANALYSIS AND MODERN SPATIOTEMPORAL CHARACTERISTICS OF TULAREMIA IN THE TERRITORY OF THE WEST KAZAKHSTAN AND NORTH KAZAKHSTAN REGIONS

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ABSTRACT

Rationale. *An important task is to monitor the incidence of tularemia among the population of Kazakhstan. Natural foci of this infection occupy large areas. In some regions with large numbers of rodents and ectoparasites and low vaccination coverage, human cases of tularemia have been reported.*

The aim of the study. *To carry out retrospective analysis and to study modern spatiotemporal characteristics of tularemia in the West Kazakhstan and North Kazakhstan regions in order to improve the effectiveness of preventive measures.*

Materials and methods. *In our work, we used public records, the results of an epizootological survey of tularemia natural foci and the official data from the Departments of Sanitary and Epidemiological Control of two regions on the human cases of tularemia in 2000–2021. We used descriptive statistics methods, relative and absolute indicators of the tularemia incidence in the population for the analysis. The phenotypic and genetic properties of the strains isolated in 2000–2021 were studied according to the guidelines.*

Results. *A retrospective analysis of the tularemia incidence among the population of the North Kazakhstan and West Kazakhstan regions showed an improvement in the epidemic situation. Over the past 20 years, 4 human cases of tularemia have been registered in the West Kazakhstan region, while the epizootic potential was quite high; more than 300 strains of the tularemia microbe were isolated during the studied period. In the North Kazakhstan region from 2000 to 2021, 11 human cases of tularemia were registered; when studying rodents, mammals and environmental objects, single positive samples for specific tularemia antibodies and antigens were detected; no strains of tularemia microbe were isolated.*

Conclusion. *An analysis of long-term data on the epizootic and epidemic activity of tularemia natural foci, processed using descriptive statistics and GIS technology, made it possible to identify places of long-term persistence of the tularemia agent in the natural focus of the North Kazakhstan and West Kazakhstan regions and to create an electronic map of the territories endemic for tularemia to determine the scope of preventive measures.*

Key words: *tularemia, natural foci, incidence, ectoparasites, rodents*

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РЕТРОСПЕКТИВНЫЙ АНАЛИЗ И СОВРЕМЕННАЯ ПРОСТРАНСТВЕННО-ВРЕМЕННАЯ ХАРАКТЕРИСТИКА ТУЛЯРЕМИИ НА ТЕРРИТОРИИ ЗАПАДНО-КАЗАХСТАНСКОЙ И СЕВЕРО-КАЗАХСТАНСКОЙ ОБЛАСТЕЙ

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РЕЗЮМЕ

Обоснование. *Важной задачей является слежение за заболеваемостью населения Казахстана туляремией. Природные очаги этой инфекции занимают большие территории. В некоторых регионах с высокой численностью грызунов и эктопаразитов и низким охватом вакцинацией регистрируют случаи заболевания людей туляремией.*

Цель исследования. *Ретроспективный анализ и изучение современной пространственно-временной характеристики туляремии в Западно-Казахстанской и Северо-Казахстанской областях для повышения эффективности профилактических мероприятий.*

Материалы и методы. *В работе использованы архивные документы, результаты эпизоотологического обследования природных очагов туляремии, официальные сведения Департаментов санитарно-эпидемиологического контроля двух областей о случаях заболевания людей туляремией в 2000–2021 гг. Для анализа использованы методы описательной статистики, относительные и абсолютные показатели заболеваемости населения туляремией. Фенотипические и генетические свойства штаммов, выделенных в 2000–2021 гг., изучали согласно методическим рекомендациям.*

Результаты. *Ретроспективный анализ заболеваемости людей туляремией в Северо-Казахстанской (СКО) и Западно-Казахстанской (ЗКО) областях показал, что в период с 2000 по 2021 г. наблюдается улучшение эпидемической ситуации. В ЗКО за последние 20 лет было зарегистрировано 4 случая заболевания людей туляремией, при этом эпизоотический потенциал довольно высокий – в рассматриваемый период выделено более 300 штаммов туляремийного микроба. В период с 2000 по 2021 г. в СКО зарегистрировано 11 случаев заболевания людей туляремией; при исследовании грызунов и млекопитающих, объектов внешней среды выявляют единичные положительные пробы на специфические туляремийные антитела и антигены, штаммы туляремийного микроба не выделены.*

Заключение. *Анализ многолетних данных по эпизоотической и эпидемической активности природных очагов туляремии, обработанный с помощью описательной статистики и ГИС-технологии, позволил выявить места длительного сохранения возбудителя туляремии в природном очаге Северо-Казахстанской и Западно-Казахстанской областей и создать электронную карту эндемичных по туляремии территории населённых пунктов для определения объёмов профилактических мероприятий.*

Ключевые слова: *туляремия, природный очаг, заболеваемость, эктопаразиты, грызуны*

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Tularemia has been reported among population in many countries around the world [1]. The tularemia microbe has taken root in Kazakhstan as a result of natural conditions favourable for carriers and vectors, as well as the possibility of *Francisella tularensis* existence in their bodies. Mammals spread the infection widely by vectors. Cases of tularemia among people are registered in almost all regions of the Republic of Kazakhstan.

Focal tularemia territories occupy huge areas in Kazakhstan – more than 550 thousand km^2. In the 1930s–1950s, there was a high incidence of tularemia among humans. Specific preventive measures contributed to the improvement of the epizootic situation. Between 1999 and 2021, 86 cases of tularemia among humans were registered in Kazakhstan.

In Kazakhstan, the landscape complex of tularemia focality is represented by foothill brook, floodplain swamp, tugai and steppe types of foci. Floodplain swamp foci are located in Pavlodar, Kostanay Akmola, Aktobe, Almaty, Atyrau, East Kazakhstan, West Kazakhstan and Karaganda regions. Foothill-brook foci are located on the territory of Almaty and East Kazakhstan regions. Tugai foci were registered in Jambyl (or Zhambyl) and Kyzylorda regions. Steppe foci are present in the West Kazakhstan and Pavlodar regions.

Different routes of transmission have been recorded in floodplain swamp areas [2]. The highest percentage of cases is recorded with vector-borne infection.

During a focus inspection in the West Kazakhstan and North Kazakhstan regions we have found high infection rate among rodents and vectors. In Kostanay, Jambyl, Karaganda, East Kazakhstan, Akmola, Aktobe and Pavlodar regions, focal tularemia territories are currently inactive. There are no foci of tularemia on the territory of Mangystau and Turkistan regions [3].

THE AIM OF THE STUDY

To carry out retrospective analysis and to study modern spatiotemporal characteristics of tularemia in the West Kazakhstan and North Kazakhstan regions in order to improve the effectiveness of preventive measures.

MATERIALS AND METHODS

In our work, we used public records, the results of an epizootological survey of tularemia natural foci and the official data from the Departments of Sanitary and Epidemiological Control of two regions on the human cases of tularemia in 2000–2021. We used descriptive statistics methods, relative and absolute indicators of the tularemia incidence in the population for the analysis. Analyses of human cases of tularemia included the study of sources, factors, routes of transmission of the *F. tularensis* and clinical forms. The phenotypic and genetic properties of the strains isolated in 2000–2021 were studied according to the methodological recommendations "On approval of methodological recommendations on strengthening measures to prevent human diseases with tularemia in the Republic of Kazakhstan" (Order of the Ministry of Health of the Republic of Kazakhstan No. 88 dated 14.12.2005).

RESULTS AND DISCUSSION

The risk of human infection with tularemia varies in Kazakhstan. This article presents a retrospective analysis and modern characteristics of tularemia in the West Kazakhstan and North Kazakhstan regions.

In the West Kazakhstan region there are foci of floodplain swamp and steppe types, which are included in zone A – active natural foci of tularemia [4]. The floodplain swamp focus covers an area of more than 100,000 km^2. *F. tularensis* strains are detected annually in the foci, and sporadic infection cases among humans are registered [5]. The floodplain swamp focus occupies 37881.8 km^2 and is located in the floodplain of the Ural River with its tributaries (Kaztalovsky, Zhangalinsky, Akzhaiksky, Terektinsky, Burlinsky districts) [6]. The steppe focus occupies an area of 91081.1 km^2 and covers the territories of seven districts of the region (Akzhaiksky, Bokeyordinsky, Zhangalinsky, Kaztalovsky, Baitereksky (formerly Zelenovsky), Taskalinsky, Chingirlausky). In the steppe focus the causative agent circulates among hamsters, hares, field and house mice, water voles; its main vectors are ixodes ticks of the *Dermacentor* genus.

The main carrier of the tularemia causative agent in floodplain swamp foci is the water vole. In the West Kazakhstan region, 22 species of wild mammals are carriers of *F. tularensis* . The ecological and faunal list of mammals susceptible to *Francisella tularensis* was expanded by four species over the twenty years from 1994 to 2021 (stoat, grey dwarf hamster, isabelline wheatear and common shrew) and increased to 26 species. In the period 2015–2021, winter epizootics with involvement of all common rodent species were registered in eight districts of the West Kazakhstan region. The main vectors are ixodes ticks of the genera *Dermacentor, Rhipicephalus, Ixodes*. In 2020, the tick population was 47.8 specimens per 1 flag-km. The most active foci are located in the middle reaches of the Ural River, along the Bolshoy and Maly Uzen rivers, and in the Ural-Kushum interfluve (Fig. 1).

High level of epidemic activity before mass tularemia vaccination in the West Kazakhstan region was noted in the early twentieth century. In 1928, the first human cases of tularemia were registered in the Ural River floodplain, which were associated with mass harvesting of water vole skins [7]. Prior to 1960, large epidemic outbreaks associated with water vole hunting were recorded

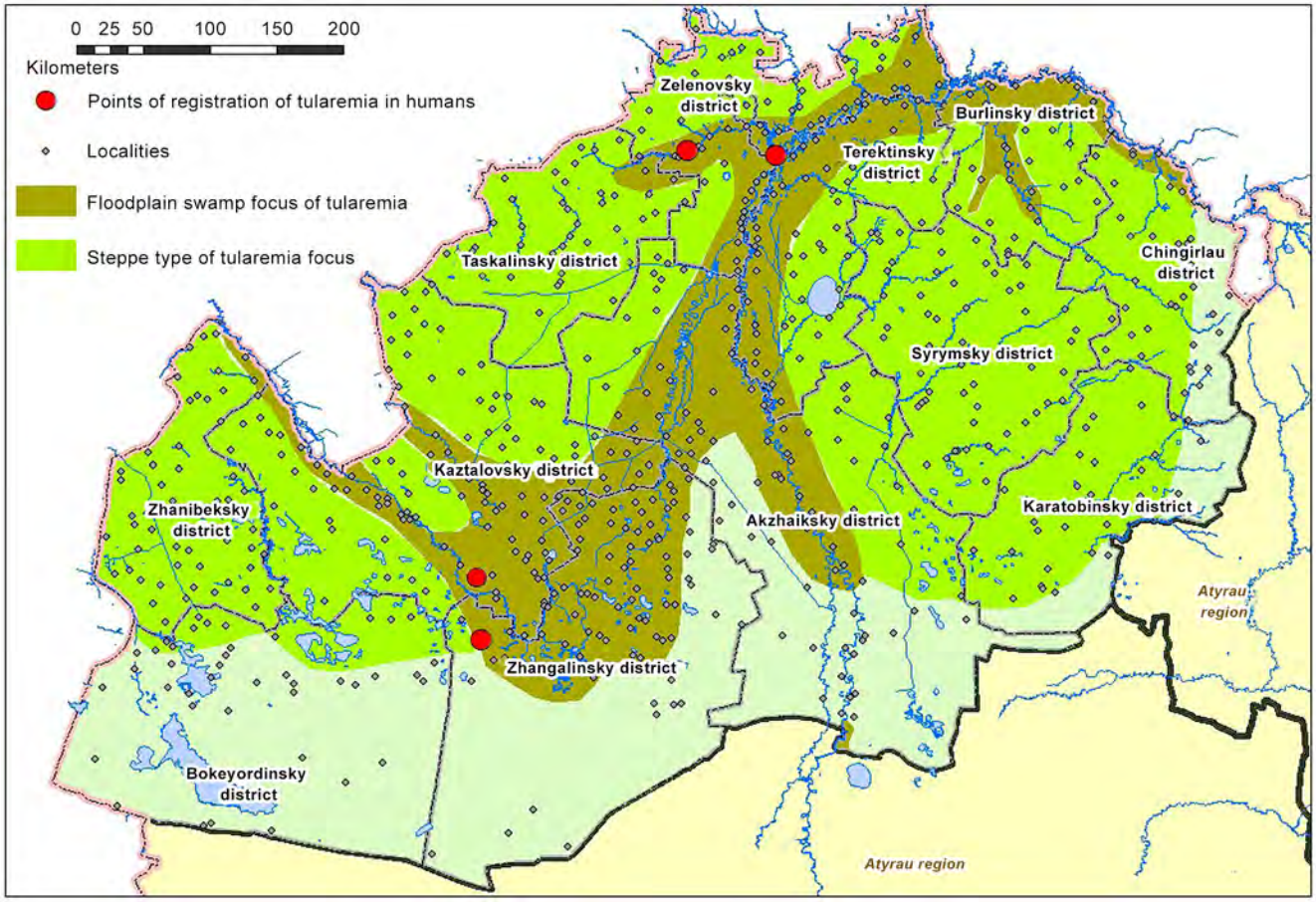

FIG. 1.
Tularemia foci in the territory of the West Kazakhstan region

in the West Kazakhstan region [8]. In 2002, a case of human tularemia in Kaztalovsky district of the West Kazakhstan region was registered. In 2007, a 26-year-old Uralsk resident fell ill with weakness, sweating, malaise, and a fever of up to 39 °C. A 4-fold increase of antibody titer in indirect hemagglutination reaction from 1:80 to 1:320, enlargement of lymph nodes was revealed, and on 18 May, 2007 the patient was admitted to the City Clinical Hospital of Infectious Diseases with the diagnosis: Tularemia, bubonic form, moderate form. An epidemiological investigation determined that there may have been contact with rodents that were in the house [9]. In 2018, 1 case of human tularemia was registered in the region, which resulted in recovery.

Analysis of human tularemia cases from 1928 to 1960 in the West Kazakhstan region showed that about 900 cases were registered in these years. 3 cases of tularemia were detected between 2000 and 2001. Since 1960, in the following 37 years the epidemiological situation in the region was favourable. The incidence of human disease in the West Kazakhstan region has decreased 200 times in the last 20 years compared to 1928–1960. At the same time, the epizootic potential is rather high: more than 300 strains of *F. tularensis* were isolated during the period. The comparative study of molecular biological properties of *F. tularensis* strains allowed to conclude both intraspecific variability and interspecific similarities. The range of genetic variability of tularemia microbe strains was determined using 25 *VNTR* markers; the strains were found to belong to the second cluster. Outbreak of foodplain swamp foci mostly assosiated by hunting of wild animals and by vector-borne transmission. The source of human infection was rodents, and the vectors were ticks of the *Dermacentor* genus. The patients had a cutaneous bubonic form of tularemia with moderate and mild severity of the infection course [10]. The incubation period averaged 3–7 days. Diagnosis was confirmed on the basis of epidemiological history, clinical manifestation and serological confirmation.

Thus, the study of the current spatial and temporal characterization of tularemia from 2000 to 2021 in the West Kazakhstan region showed that the epidemic potential of tularemia has significantly decreased.

On the territory of the North Kazakhstan region there are active natural foci of tularemia; endemic territories

are Mamlyutsky, Kyzylzhar, Magzhan Zhumabaev, Gabit Musrepov, Ayyrtau, Shal Akyn, Akkayynsky districts (Fig. 2). Tularemia epizootics were registered in the floodplain of the Ishim River, which crosses the region from south-west to north-east, and its tributaries [11]. The main carrier of the tularemia microbe in the floodplain swamp foci is the water vole (50 specimens per 1 km of coastline, 0.4–2.8 % infection rate). The epizootic process involves rodents and vectors – ticks of the *Dermacentor* genus. Periods of high water vole population were recorded in 1927–1929, 1937–1939, 1947–1949, 1952–1953, 1957–1958.

For the first time in 1958, a culture of the *F. tularensis* was isolated from a muskrat. In 1972, a spillover epizootic was registered in Akkayynsky, Zhambyl, and Mamlyutsky districts. In 1972, 12 strains of the tularemia agent were isolated from a field mouse and a water vole; in 1973 a strain was isolated from *D. marginatus ticks*. In the following years, serological confirmation of the epizootic process was obtained almost annually.

In 1945, 8 cases of human tularemia were registered in the North Kazakhstan region for the first time. In 1949, 200 human cases were reported. In 1972, there was a major outbreak of tularemia, affecting more than 40 people. The outbreak was transmissible and occurred in the vicinity of Petropavlovsk, Sokolovsky and Mamlyutsky districts.

As a result of retrospective analysis, it was determined that from 1945 to 1999 in the North Kazakhstan region 441 cases of tularemia among people were registered. Human infections were observed in summer, during the period of activity of blood-sucking two-winged insects, and clinically manifested in ulcerative and bubonic form [12].

Between 2000 and 2021, 11 human cases of tularemia have been reported. Infection of people occurred in the territory endemic for tularemia (Akkayynsky, Kyzylzhar, Magzhan Zhumabaev districts). The source was rodents, the transmission factors were arthropods, and the routes of transmission were contact and vector-borne.

A study of the contemporary spatial and temporal characterization of tularemia showed that the intensity of epizootics from 1945 to 1999 was high. *Fr. tularensis* strains were isolated during rodent and arthropod surveys. In recent years (2000–2021), single positive samples for specific tularemia antibodies and antigens have been detected in rodents, mammals and environ-

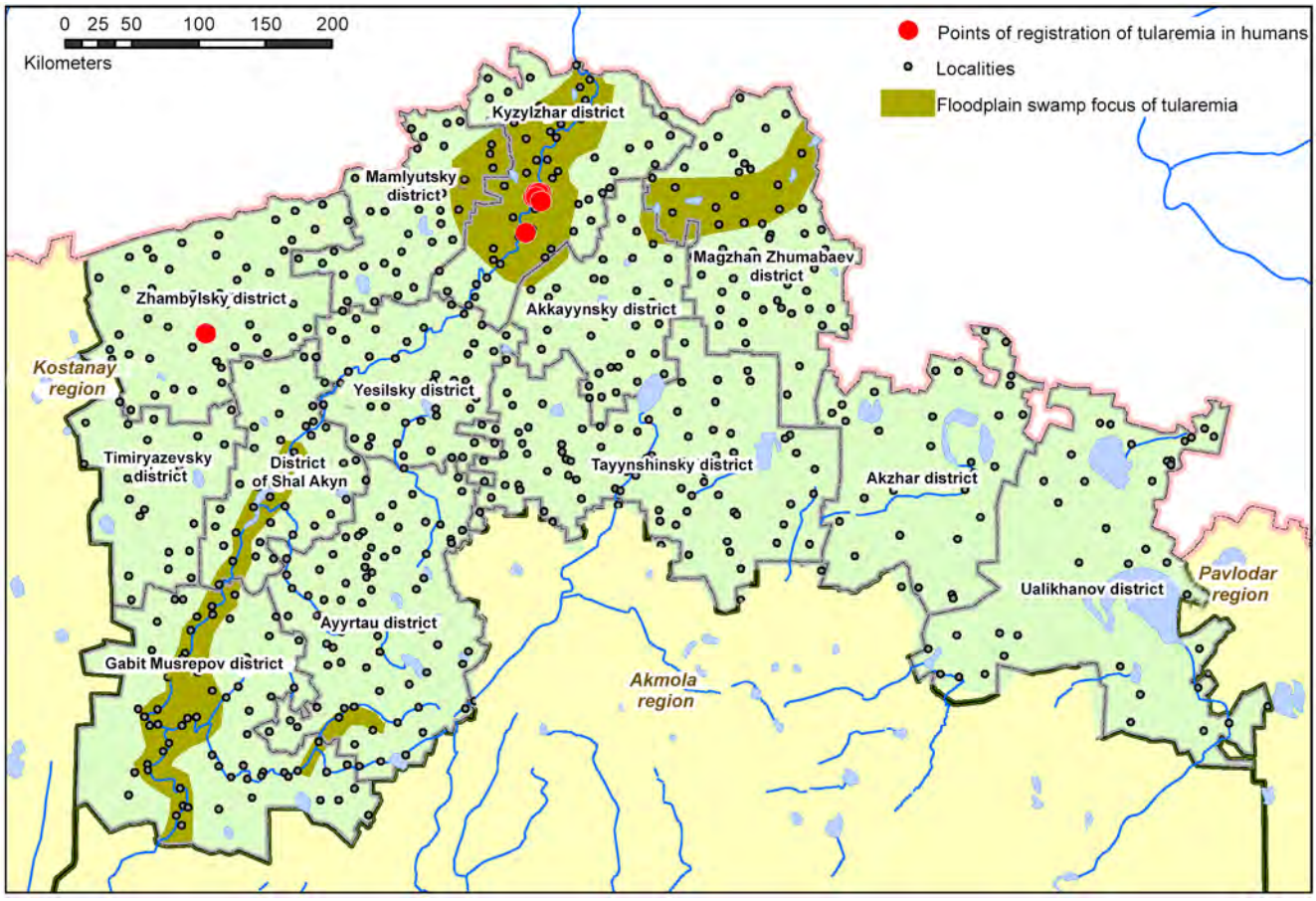

FIG. 2.
Tularemia foci in the North Kazakhstan region

TABLE 1

RELATIVE INCIDENCE RATE OF THE POPULATION FROM 2000 TO 2021 IN THE WEST KAZAKHSTAN AND NORTH KAZAKHSTAN REGIONS

Regions of Kazakhstan	Years of human cases of tularemia (relative indicator)						
	2002	2003	2004	2006	2007	2016	2018
West Kazakhstan Region	0.17	0	0	0	0.16	0.2	0.16
North Kazakhstan Region	0.15	0.59	0	0.3	0	0.2	0.18

mental objects; *Fr. tularensis* strains have not been isolated.

A study of the current spatial and temporal characterization of tularemia (2000–2021) in the North Kazakhstan region showed that the epidemic potential has significantly decreased. The incidence among humans between 2000 and 2021 decreased 39-fold compared to the period between 1945 and 1999. The relative incidence of human tularemia in the period 2000–2021 is shown in Table 1, which presents the years when human tularemia cases were registered.

Contact of the population with rodents infected with tularemia, consumption of water and food contaminated with *F. tularensis* causative agent and tick bites are the main causes of infection and disease among humans. Before 2000, the source of infection and factors of causative agent transmission were muskrat hunting, water and blood-sucking two-winged insects; after 2000, the main type of transmission was alimentary.

CONCLUSION

An analysis of long-term data on the epizootic and epidemic activity of tularemia natural foci, processed using descriptive statistics and GIS technology, made it possible to identify places of long-term persistence of the tularemia agent in the natural focus of the North Kazakhstan and West Kazakhstan regions and to create an electronic map of the territories endemic for tularemia to determine the scope of preventive measures.

A study of the current spatial and temporal characterization of tularemia (2000–2021) in the West Kazakhstan and North Kazakhstan regions showed that the epidemic potential has significantly decreased.

Characteristic epidemiological features of this period are single cases of the disease with infection in floodplain swamp natural foci; predominantly alimentary route of infection through consumption of food or water contaminated with tularemia.

In the West Kazakhstan and North Kazakhstan regions, no significant changes in the epizootic situation are currently expected, but there is a risk of sporadic cases of morbidity among the population. Under favorable conditions for increasing numbers of rodents, ticks and blood-sucking insects, the epizootic process may intensify to local and spillover epizootics.

It is necessary to continue monitoring studies and to carry out timely preventive measures, including vaccination of the population.

Conflict of interest

The authors declare the absence of any conflict of financial/non-financial interests related to the article.

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Authors' contributions

Uinkul A. Izbanova – study of archival and official documents, results of epizootological survey of natural foci of tularemia in two regions; literature search on epidemiological monitoring of tularemia in natural foci of Kazakhstan in PubMed, Thomson Reuters, Springer, eLibrary databases; analysis of data on the incidence of tularemia using descriptive statistics, relative and absolute indicators.

Larisa Yu. Lukhnova – literature review, assessment of the reliability of data in selected sources; analysis of tularemia incidence using descriptive statistics methods; conclusion to the article.

Tatyana V. Meka-Mechenko – literature review; search for archival documents in the scientific library of National Scientific Center of Especially Dangerous Infections named after Masgut Aikimbayev.

Nurbek S. Maykanov – study of archival and official documents, results of epizootological survey of natural foci of tularemia in the West Kazakhstan region.

Veronika P. Sadovskaya – formation of shapefiles and creation of GIS-map of tularemia foci in the North Kazakhstan and West Kazakhstan regions.

Vladimir G. Meka-Mechenko – search for archived data on the results of epizootological survey of the territory of two regions for tularemia.

Aisazhan A. Yusupov – study of archival and official documents, results of epizootological survey of natural foci of tularemia in the North Kazakhstan region; study of properties of the tularemia microbe strains isolated in 2000–2021.

Akbota B. Makulova – study of archival and official documents, results of epizootological survey of natural foci of tularemia in the West Kazakhstan region; study of properties of the tularemia microbe strains isolated in 2000–2021.