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## EPIDEMIC PROCESS OF TULAREMIA IN THE WORLD AND IN THE SOUTH OF UKRAINE

G. Jurtubaeva, A. Savchuk, O. Kozishkurt, O. Gerasimenko, V. Gaidei, L. Kostolonova

The Odessa National Medical University, Ukraine

### Abstract

Present day tularemia prevalence in the world and in Ukraine is described as well as the current epidemic and epizootic situation in various regions. The mechanisms of transmission of the pathogen are discussed. The causative agent of tularemia *Francisella subsp. tularensis* is one of the most virulent microorganisms of the highest priority (category "A"). This can be used as a biological weapon, and so poses a real threat to the humanity's security. Human infection occurs as a result of bites by infected blood-sucking arthropods (mosquitoes, thrips, ticks), consumption of rodent-contaminated food and water, inhalation of air-dust aerosol from diseased rodents contaminated with the pathogen, and also after direct contact with infected animals (hunting, caring for pets, carcass processing). Isolates of the most virulent for humans and animals subspecies *F. tularensis subsp. tularensis* circulate only in North America. The less virulent subspecies *F. tularensis subsp. Holarctica* circulates in North America, Europe, Asia (Japan), Australia (including Tasmania). The wide distribution of this subspecies in the world is due to its ability to exist in the aquatic environment. In most European countries, the terrestrial cycle of existence of the tularemia microbe is dominant, in the body of small mammals and carriers of the pathogen - mosquitoes, ticks, and whiteflies. The main clinical form of tularemia is ulcerative-bubonic, it is quite easily diagnosed, infection occurs as a result of bites by infected blood-sucking arthropods. Anginal-bubonic

and gastrointestinal forms are diagnosed in hot countries, they are associated with the consumption of food and water contaminated by rodents. In the nearest future the worsening of tularemia epidemic situation in various regions of the world is predicted due to the activation of enzootic centers and lack of vaccination of risk groups persons and the population of endemic areas.

**Key words: tularemia; morbidity; epidemic situation; epizootic situation.**

Tularemia is a particularly dangerous zoonotic infection that has a natural focal character, numerous carriers and vectors, and various ways of transmission [1]. The infectious dose of *F. subsp. tularensis* for humans at aerogenous infection is only 10 microbial cells, and susceptibility to the pathogen reaches 100%. Ecological plasticity, ability to long-term persistence of *F. tularensis subsp. holarctica*, polyhostality, persistence of natural foci of tularemia causes periodic epidemic complications of various scales - from sporadic cases to group morbidity and outbreaks [2].

The most virulent for humans and animals is the subspecies *F. tularensis subsp. Tularensis*, the less virulent is subspecies *F. tularensis subsp. Holarctica*. Isolates of this subspecies are found in the territories of different climatic zones - from subarctic to subtropical, the biocenoses of natural foci are the most diverse - from aquatic to desert, with hosts and vectors of their own. The wide prevalence of this subspecies strains all over the world, in comparison with other subspecies of tularemia causative agents is associated with its ability to exist in the aquatic environment, which significantly expands this subspecies distribution area and shows its higher ecological plasticity and stability [3, 4].

*Francisella tularensis*, the etiological agent of tularemia, is a facultative intracellular pathogen that causes severe disease in animals and humans, and is bioterrorism agent of category A [5]. Currently, *F. tularensis* is divided into four subspecies: *F. tularensis subsp. tularensis (nearctica)*, *F. tularensis subsp. holarctica*, *F. tularensis subsp. mediasiatica*, *F. tularensis subsp. novicida*, which differ in their pathogenicity and geographical distribution. Historically, this division was due to the different range of circulation of strains, their differences in biochemical activity and pathogenicity for different hosts [6, 7]. *F. novicida* is officially recognized as the fourth subspecies of the species *F. tularensis*, has high DNA homology with other subspecies of *F. tularensis*, but is not the pathogen of typical tularemia infection. Highly virulent strains of *F. tularensis subsp. tularensis* (type A) are common only in North America, and less pathogenic strains of *F. tularensis subsp. holarctica* (type B) circulate mainly in the Northern Hemisphere. *F. tularensis subsp. mediasiatica*'s virulence is

close to *F. tularensis subsp. holarctica*, but geographically it is limited only to Central Asia. However, the expansion of its range of habitat with the isolation of strains on the territory of the Russian Federation was recently discovered [8]. *F. tularensis subsp. novicida* belongs to a subspecies that is weakly pathogenic for humans, it is occasionally isolated in North America and once was found in Australia [9].

Two subspecies virulent for humans circulate in North America - *F. tularensis subsp. tularensis* and *F. tularensis subsp. holarctica*. Within the most virulent for humans subspecies of *F. tularensis*, two populations are distinguished by genotype, geographical distribution, preferred hosts and vectors: A.I and A.II. Group A.I is further divided into subpopulations A.Ia and A.Ib. More virulent strains of A.I are found mainly in the central and eastern states of the United States of America, and A.II - in the western states. Strains of *F. tularensis subsp. tularensis* A.I more often infect ticks of the species *Amblyomma americanum* and *Dermacentor variabilis* and hares of the species *Sylvilagus floridanus*. A.II is more often associated with ticks of the *Dermacentor andersoni* species, deer fly *Chrysops discalis* and hares of the *Sylvilagus nuttallii* species [10].

The highest tularemia incidence was recorded in the USA in 1939 – 2291 cases, and usually 150 - 200 cases are recorded annually. In 2015 314 tularemia patients were registered, in 2016 – 230, and in 2017 – 239 (incidence rate is 0.07 per 100.000 of population). During 2001-2010, 1.208 cases of tularemia with 6 fatalities were registered in the USA. 68.3% of cases were caused by strains of *F. tularensis subsp. tularensis*. Mainly (67.4%) infection occurred as a result of a tick or deer fly bite, as well as (32.6% of cases) through contact with a sick or dead animal. More than half of all tularemia cases were reported in the states of Missouri, Arkansas, Oklahoma, Kansas, Nebraska and South Dakota. The peak of tularemia morbidity among humans in the USA is observed in late spring - early summer, which coincides with the activation of tick adults and nymphs that have overwintered [11].

Recently, mandatory registration of tularemia has been carried out in 31 countries of Europe and Japan in connection with the possibility of using the pathogen as an agent of bioterrorism. On average in Europe, the incidence rate per 100.000 of population varies from 0.1 to 0.3 [12, 13]. Sweden and Finland, Norway, Hungary, the Czech Republic, Germany, France, Slovakia, Poland and Spain are the leaders in incidence. These countries account for more than 95% of tularemia cases in Europe. In recent years, an additional significant contribution to morbidity in Europe is made by Switzerland and Kosovo, in which there is no mandatory registration of this disease. Single cases are registered annually in Austria, Belgium, Bulgaria, Croatia, Italy, Estonia, Lithuania, the Netherlands, Romania and Slovenia.

Countries free from tularemia in Europe are Cyprus, Greece, Iceland, Ireland, Luxembourg, Macedonia, Malta, Great Britain, where only imported cases are registered.

On the territory of Europe, isolates of the *holarctica* subspecies are mainly isolated. In most European countries, the terrestrial life cycle of the tularemia microbe is dominant, with arthropods as vectors (mainly ticks of the *Ixodes ricinus* species), small rodents (*Microtus arvalis*) and hares (*Lepus europaeus*), to which the hosts are sensitive [14-19]. Also, strains of the causative agent of tularemia are isolated from rabbits, muskrats, beavers, wild birds and domestic dogs. Despite the lack of data on transovarial transmission of tularemia pathogen by arthropods, it has been shown that the pathogen is able to be transmitted from a larva to a nymph and an adult in a 3-year cycle of *I. ricinus* ticks [20, 21].

Direct contact with infected animals is the main transmission route in Central and Southern Europe. The most common form of tularemia is gastrointestinal (typhoid), which is very difficult to diagnose due to the presence of symptoms similar to the symptoms of many other diseases [22]. In Northern Europe, the main form of tularemia is ulcerative-bubonic, it is quite easily diagnosed, infection occurs as a result of bites by infected blood-sucking arthropods (mosquitoes, flies, ticks) [23].

The main route of tularemia infection in Turkey, Bulgaria and Kosovo is alimentary, associated with the consumption of rodent-contaminated food and water. The most common forms of tularemia are anginal-bubonic (oropharyngeal) and gastrointestinal (typhoidal) [24].

The peak of tularemia in Finland and Sweden is registered in August-September, during the mass flight of insects, or immediately after it. The peak of human disease is usually preceded by the peak of reproduction of the voles population. Pollution of the environment with dead rodents, especially numerous water bodies in these countries, causes mass infection of mosquito larvae and adults [25].

The largest epidemic occurred in Sweden in 1967, when 2,700 cases of tularemia were registered [26]. In 2010, in Sweden, 78 people fell ill with the respiratory form of tularemia, one person died. Since 1984, based on epidemiological data, seven areas with a high risk of tularemia have been identified in Sweden: Örebro, Karlstad, Västerdalarna, Okelbo, Ljusdal, Östersund and Boden. The largest number of cases is recorded in Örebro area, but Okelbo, Västerdalarna and Ljusdal are leading in terms of intensive indicators.

From mid-summer 2019, data on tularemia cases began to arrive from Sweden. By October, 979 patients from 15 municipalities of the country were registered. The largest number of patients were infected in the provinces of Dalarna (252 cases), Gävleborg (147), Örebro, Västerbotten. In August, the detection of dead mountain (*Lepus timidus*) and brown

(*L. europaeus*) hares in the provinces of Dalarna, Norrbotten and Västra Götaland indicated a high degree of epizootic activity and the risk of population infection in these territories [27].

In Finland, in endemic areas, general practitioners often treat diseases only on the basis of clinical diagnosis, and laboratory-confirmed cases of tularemia account for no more than 10% of all patients in the country [28]. Ulcerative-bubonic tularemia as a result of insect bites is the main, quite easily diagnosed and with typical symptoms form of the disease. Peaks in vole populations were found to be prerequisites for tularemia outbreaks the following year. The most cases of tularemia are registered in three provinces - in Northern and Southern Ostrobothnia and Central Finland [29].

An outbreak of tularemia (180 cases) was registered in Norway in 2011, the morbidity rate was 3.7. It was associated with an increase of lemmings population and the infection's prevalence among them. From January to April, 57 cases of anginal and bubonic tularemia were registered as a result of water use from private wells. From May to September there were 40 cases of bubonic and bubonic ulcerative tularemia, 15 of which (37.5%) were associated with insect bites, the rest - 83 registered cases of anginal-bubonic, bubonic and ulcerative-bubonic tularemia were associated with the disease arose after contact with sick lemmings. 18 cultures were isolated from the patients [29].

Tularemia is endemic in Hungary. Several dozen cases of the disease are registered annually, the morbidity rate varies from 0.15 to 1.4. The pathogen is the infected free-living European brown hares (*L. europaeus*), rodents (*Apodemus flavicollis*, *Apodemus agrarius*, *M. arvalis*, *Rattus rattus*), ticks of the species *I. ricinus*, *D. reticulatus* and *Haemaphysalis concinna* [30, 31]. Monitoring of the epidemic and epizootological situation of tularemia in the country showed a high positive correlation of morbidity with the number of mice (*M. arvalis*) and the number of seropositive hares (*L. europaeus*) [32, 33].

The first outbreak of tularemia in the former Czechoslovakia was detected in the region of South-Eastern Moravia in 1936-1937. Over 400 cases were diagnosed during this outbreak. All affected people were in contact with hares. The most active are natural centers in the territories of South Moravia and Central Bohemia. From 1996 to 2011, about 100 cases of the disease were registered in the country annually, and in recent years - from 40 to 60 cases. The main patients were persons who contacted with infected hares and the workers of sugar factories [34-36].

Since 2002, tularemia in France is an infection that is subject to mandatory registration due to the possibility of using the pathogen as an agent of bioterrorism. From 2002 to 2012, 433 cases of the disease were registered in the country in persons aged 2 - 95 years old

(average age - 49 years), the ratio of men to women was 1:8. The most frequent clinical forms of the disease were bubonic (200 cases, 46%) and ulcerative-bubonic tularemia (113 cases, 26%). The main source of infection in France is exposure to dust during outdoor recreation (217 cases, 50%) and contact with animals during hunting and processing carcasses of infected hares (179 cases, 41%). Tick bites while outdoors were noted by 82 patients (19% of the total). Diseases are recorded throughout the year: infection during hare hunting - maximally in winter, from tick bites - in spring, during work and recreation in the fresh air - in summer [34, 37].

The second major human outbreak (507 cases) occurred in Spain in 2007 and 2008 and coincided with the peak of the common vole (*M. arvalis*) head count. In Switzerland, as well as in other European countries, a trend towards an increase in tularemia morbidity rate has recently been noted. If in the period from 1987 to 2012, an average of 7 cases per year were registered, then in the following years there were 30-40 cases. In 2016, 56 cases of tularemia were recorded in the country, in 2017 – 132, and in 2018 – 112 [38].

In Ukraine, natural foci of tularemia infection are widespread throughout the territory. They are characterized by stability, long-term functioning and the ability to create favorable conditions for the accumulation of infectious material, thereby creating a potential threat to the population living in endemic areas. The distribution of natural foci in the country is uneven and depends on various climatic and ecological factors affecting the biocenotic relationships between the causative agent of tularemia and numerous pathogens and carriers of the infection. A large number of natural foci of tularemia have been recorded on the territory of the country, of which the most active are in the Volyn, Rivne, Poltava, Chernihiv, Sumy, and Odessa regions.

From 1941 to 2008, the causative agent of tularemia in Ukraine was most often detected in arthropods (n = 2045; 66.3%), in mammals (n = 619; 20.1%), in water (n = 393; 12.7%) and agricultural products (n = 29; 0.94%). A total of 3.086 isolates of *F. tularensis subsp. holarctica* were obtained on the territory of Ukraine in 1084 geographical points. The main hosts of the pathogen are the vole (*Microtus arvalis*) and the field mouse (*Apodemus agrarius*), and the agents and carriers are ticks *D. marginatus*, *D. reticulatus* and *I. ricinus* [39]. Vaccination against tularemia stopped in the country in 2000.

On the territory of 11 districts of Odessa region, 46 natural foci of tularemia of various types were registered in previous years: 30 foci of field (meadow-field), 7 - forest, 5 - floodplain-swamp. After 1998, 4 steppe-type areas were discovered in the Comintern district.

In natural areas, ecological interactions are preserved in the formed parasitic biocenosis and intra-areal connections. Under such conditions, the natural focus of tularemia as a complete parasitic system exists for a long time without noticeable changes, manifesting itself with the help of epizootics among the main and secondary carriers of the pathogen, which should include, first of all, the house mouse *Mus musculus*, the mound mouse *Mus spicilegus*, the vole common *Microtus arvalis*, gray hamster *Cricetulus migratorius*, common hamster *Cricetus cricetus*, and gray hare *Lepus europaeus*. Wide spread of infection in the steppe zone was facilitated by spilled epizootics of tularemia among small mammals and favorable climatic conditions for their mass reproduction [39].

In recent years (2015-2017), on the basis of ecological, epizootological and microbiological studies, the circulation of *F. tularensis* among certain species of small mammals (wood mouse *Sylvaemus sylvaticus*) and ixod ticks (*Dermacentor marginatus*, *Rhipicephalus rossicus*) was established. During the serological examination of the predatory birds pellets, the antigen of the causative agent of tularemia was detected in the bone remains of 4 species of small mammals: wood mouse (*Sylvaemus sylvaticus*, yellow-throated mouse (*Sylvaemus tauricus*), mound mouse (*Mus spicilegus*), meadow vole (*Microtus levis*).

Considering the large number of geographical areas in the world that are enzootic for tularemia, the current epizootological situation, the cessation of vaccination of persons with occupational risk of the disease and the population of many endemic areas of the world, it is possible to predict the complications of the epidemic situation of tularemia infection.

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