TULAREMIA

Tularemia

also known as rabbit fever, is an infectious disease caused by the bacterium *Francisella tularensis*.

Symptoms may include fever, skin ulcers, and enlarged lymph nodes.

Occasionally, a form that results in pneumonia or a throat infection may occur.

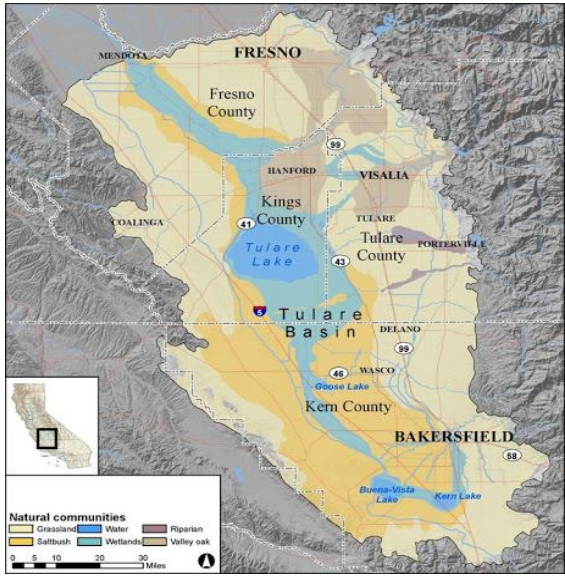
Tularemia is primarily a disease of wild animals and persists in contaminated environments, ectoparasites, and animal carriers.
Human infection is incidental and responsible for a number of syndromes that range from a plague-like ulceroglandular illness to pneumonia.

BRIEF HISTORICAL INFORMATION

In 1910, in the area of Lake Tulare in California D. McCoy discovered a disease in ground squirrels resembling a bubonic plague in the clinical picture. Soon after, he and Ch.Chaplin isolated a causative agent from sick animals, which was called Bacterium tularense (1912).

Later it was found out that people are susceptible to this infection, and, at the suggestion of E. Francis (1921), she was called tularemia.

Later, the causative agent was named after Francis, who studied him in detail.



Etiology

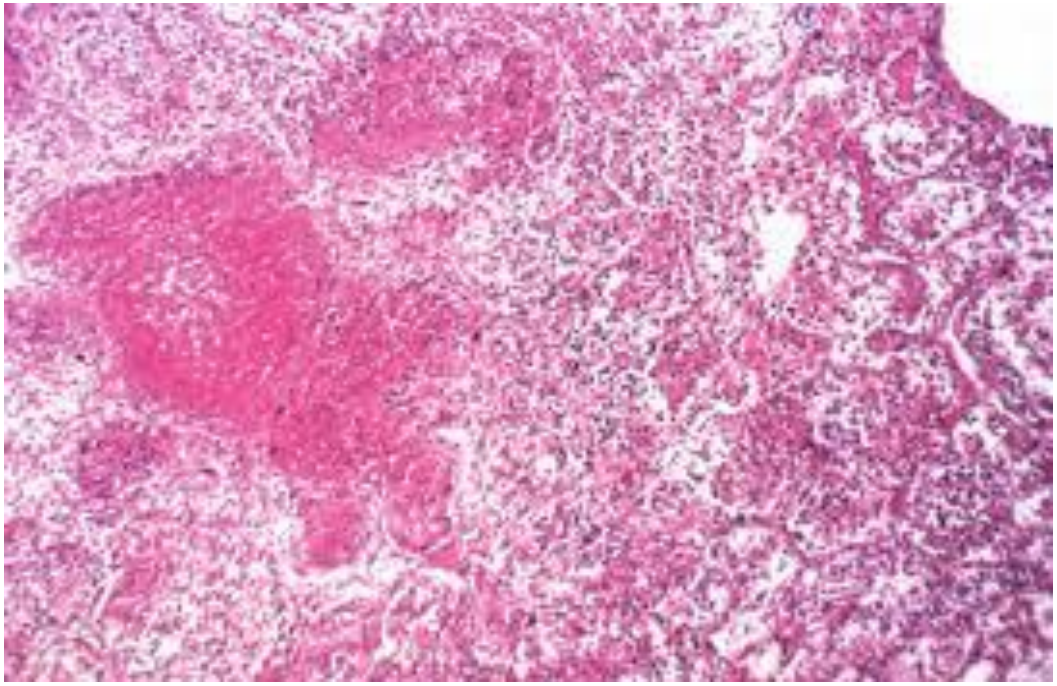
Tularemia is caused by *Francisella tularens* - the genus Francisella of the Brucellaceae family.

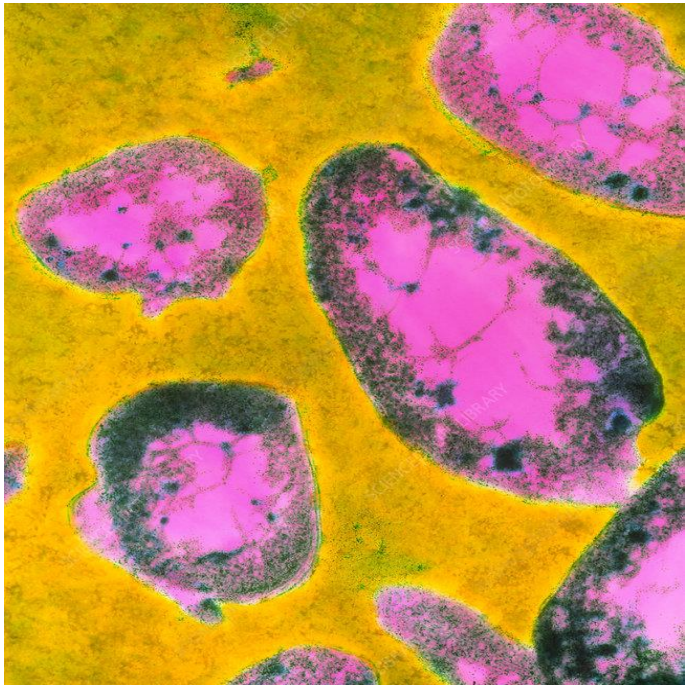
- **a small (0.2 μm by 0.2–0.7μm),**
- **gram-negative,**
- **pleomorphic,**
- **nonmotile,**
- **non-spore-forming bacillus.**

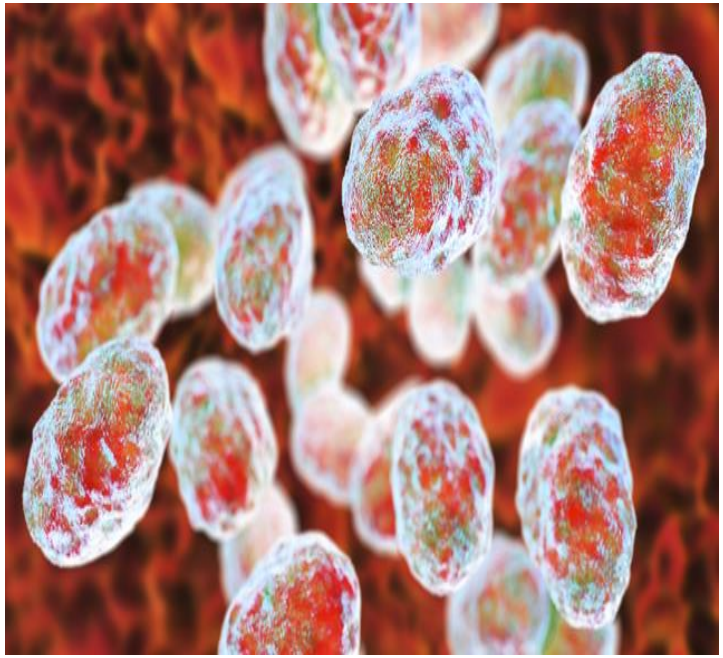
They are more uniformly rod-shaped during logarithmic growth, during which they tend to exhibit bipolar staining with Gram or Giemsa methods.

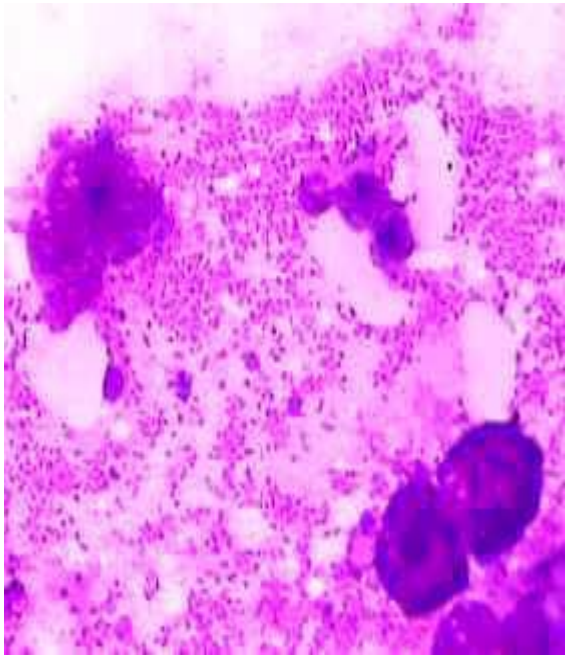
The organism is virulent, and small numbers of organisms on the skin can invade and lead to systemic illness.

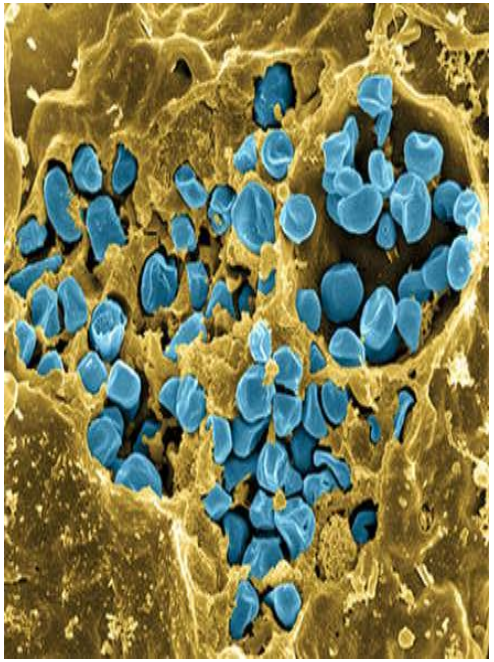
***F. tularensis* is resistant to freezing and may persist for weeks in dead animals, is inactivated by heat.**

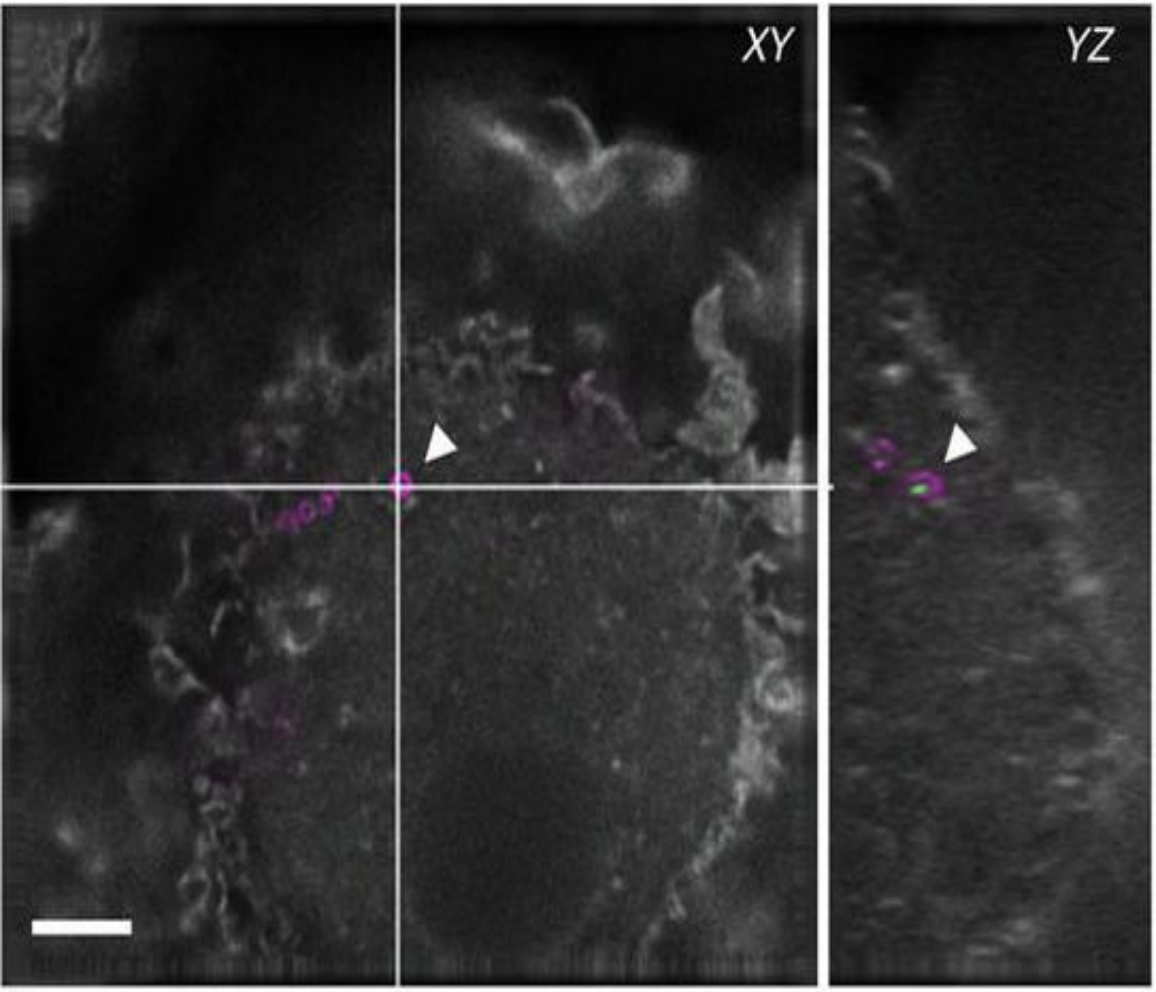


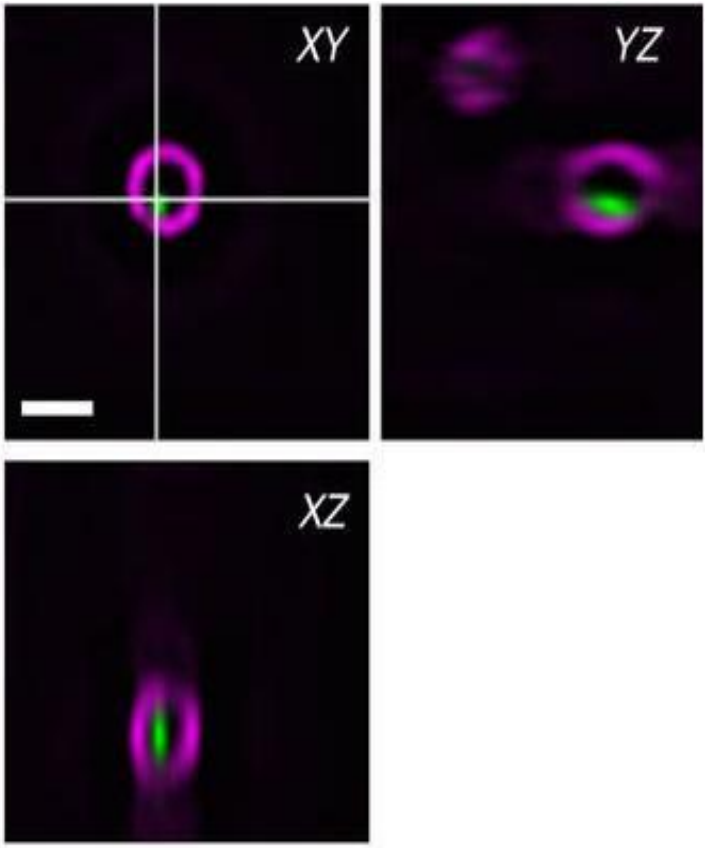


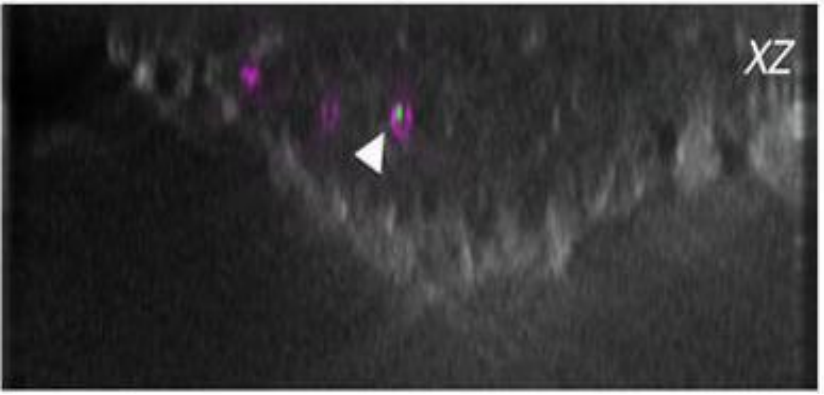












Francisella bacteria inside macrophage (purple).

In serological reactions, cross react with Brucella and Yersinia. There are two types of pathogen.

Type A –*tularensis*- causes more severe forms of the disease in humans and is pathogenic for rabbits,
without treatment, the associated fatality rate is ~5%.
It occurs only in North America.
It is considered as a probable bacteriological weapon.

Type B - *holarctica* - is found in North America, Europe and Asia.
It causes lighter human diseases, does not ferment glycerin and citrulline, and is not pathogenic for rabbits (when infected with type A pathogens, rabbits die with even 1 microbial cell, type B - 1 billion cells).

Holarctic (European-Asian). Includes three biological options:

Japanese biovar

Erythromycin -sensitive

Erythromycin -resistant

Intraspecific differentiation of the pathogen of tularemia is based on differences in subspecies and biovars for a number of phenotypic traits:
biochemical activity,
the composition of higher fatty acids,
the degree of pathogenicity for humans and animals, the sensitivity to certain antibiotics,
as well as the features of ecology and the area of the pathogen.
O- and Vi-antigens are found in bacteria.
Bacteria grow on yolk or agar media with the addition of rabbit blood or other nutrients.
From laboratory animals, white mice and guinea pigs are susceptible to infection

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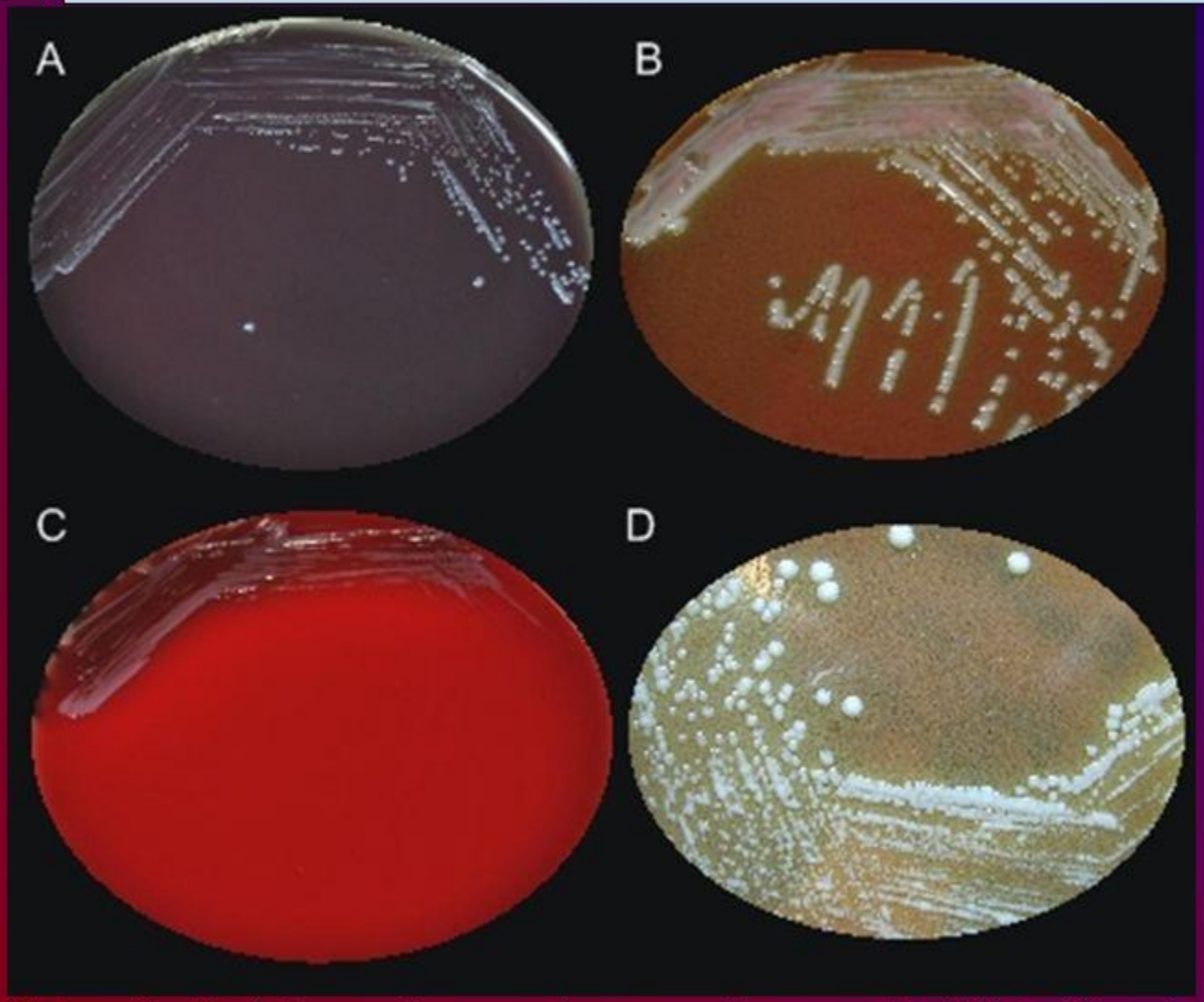
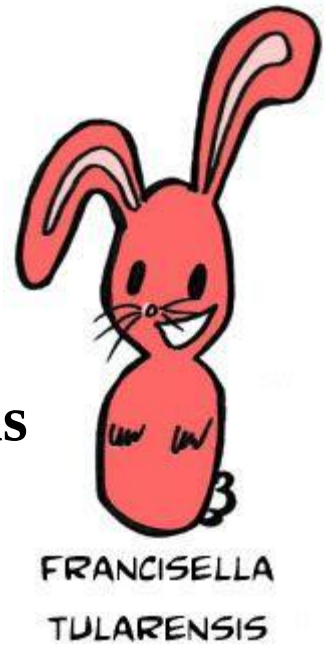
Francisella tularensis



Colonization of *Francisella tularensis* on various media, namely: (A) buffered charcoal yeast extract; (B) chocolate agar medium; (C) sheep's blood agar; (D) cysteine heart agar.

Outside the host organism the pathogen persist for a long time.

Thus, in water at 4 ° C it retains its viability for 1 month, on straw and grain at a temperature below 0 ° C - up to 6 months, at 20-30 ° C - up to 20 days, in skins of animals fallen from tularemia, at 8 -12 "C - more than 1 month.

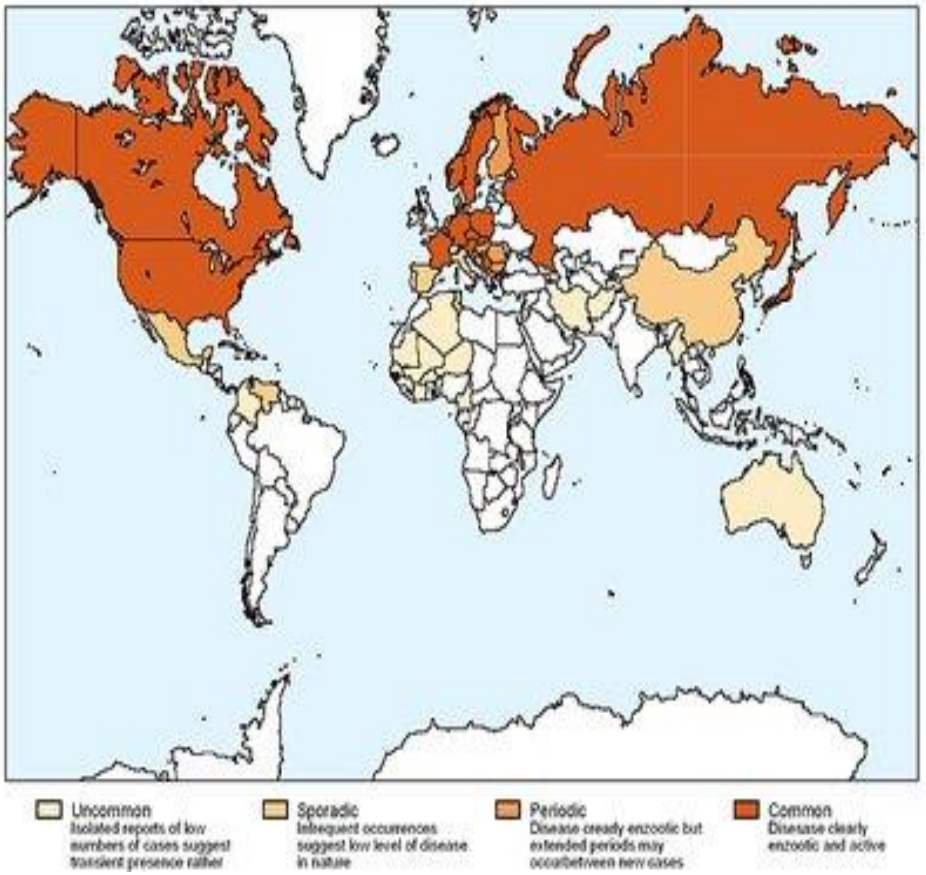


Bacteria are unstable to high temperatures and disinfectants.

For disinfection, 5% phenol solution is used, the solution is 1: 1000 (kills bacteria for 2-5 minutes), 1-2% formalin solution (kills bacteria in 2 hours), 70 ° ethyl alcohol, etc.

For complete disinfection of the corpses of infected animals, they should be kept for at least 1 day in a disinfectant solution, after which it should be autoclaved and incinerated.

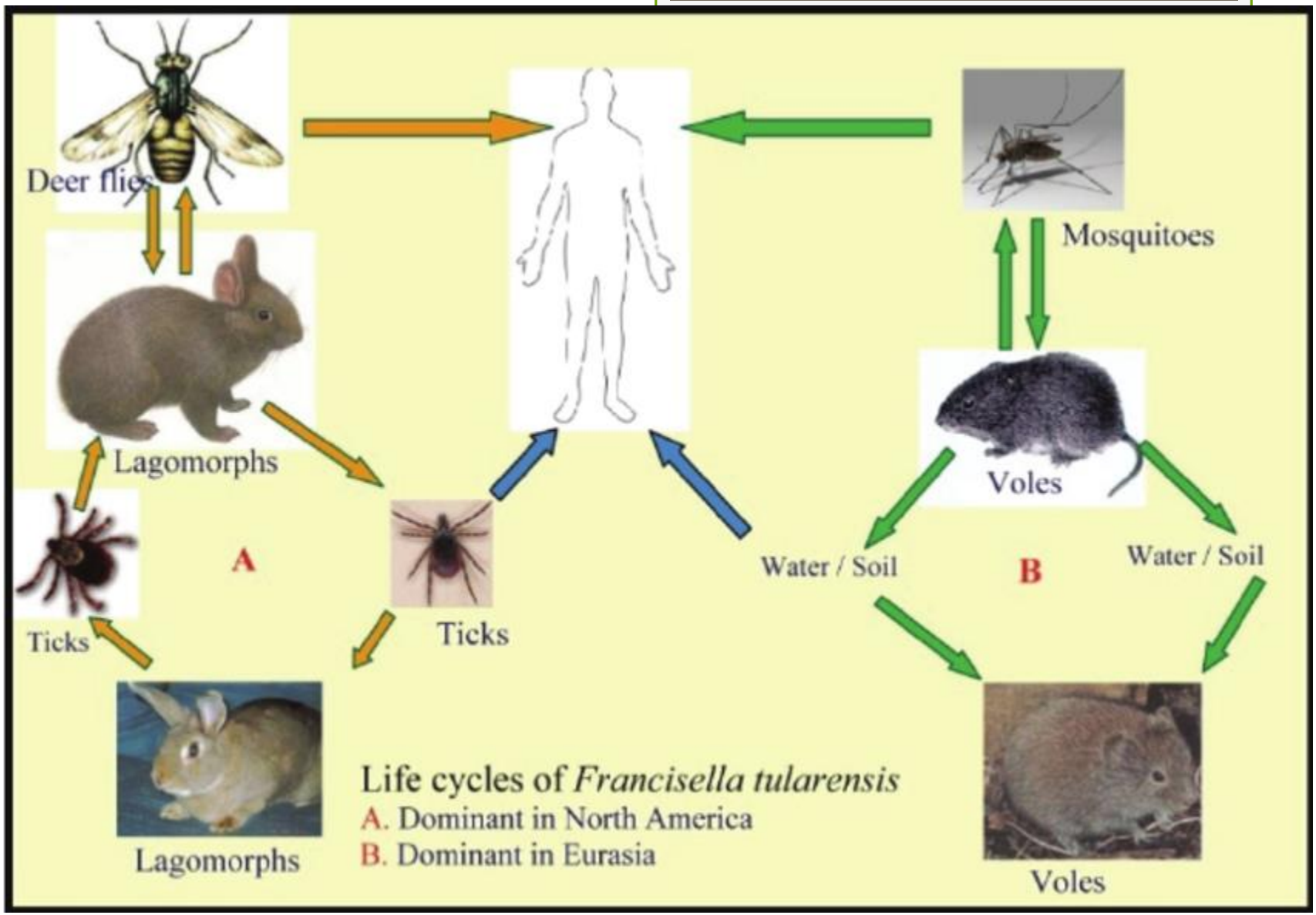
Epidemiology



Tularemia is a widespread natural focal disease that occurs mainly in the landscapes of the temperate climatic belt of the Northern Hemisphere. It is widely distributed in Europe, America and Africa.

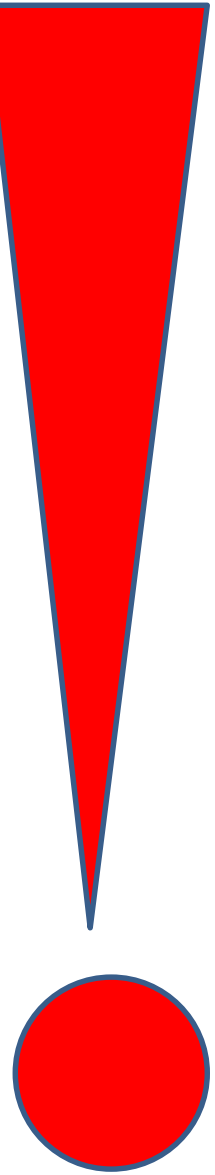
The reservoir and source of infection are numerous species of wild rodents, lice, birds, dogs, etc.
Bacteria are isolated from 82 species of wild, as well as from domestic animals (sheep, dogs, artiodactyls).
The main role in maintaining the infection in nature belongs to rodents (water rat, common vole, muskrat, etc.)

A sick person is not dangerous to others.


Deer flies
Mosquitoes
Lagomorphs
Voles
A
Ticks
Ticks
Water / Soil
B
Water / Soil
Lagomorphs
Voles
Life cycles of *Francisella tularensis*
A. Dominant in North America
B. Dominant in Eurasia

The causative agent persists in nature in the tick-animal cycle, it is transmitted to agricultural animals and birds by ticks and blood-sucking insects. Specific carriers of tularemia are ixodid mites.

The natural susceptibility of people is high (almost 100%).

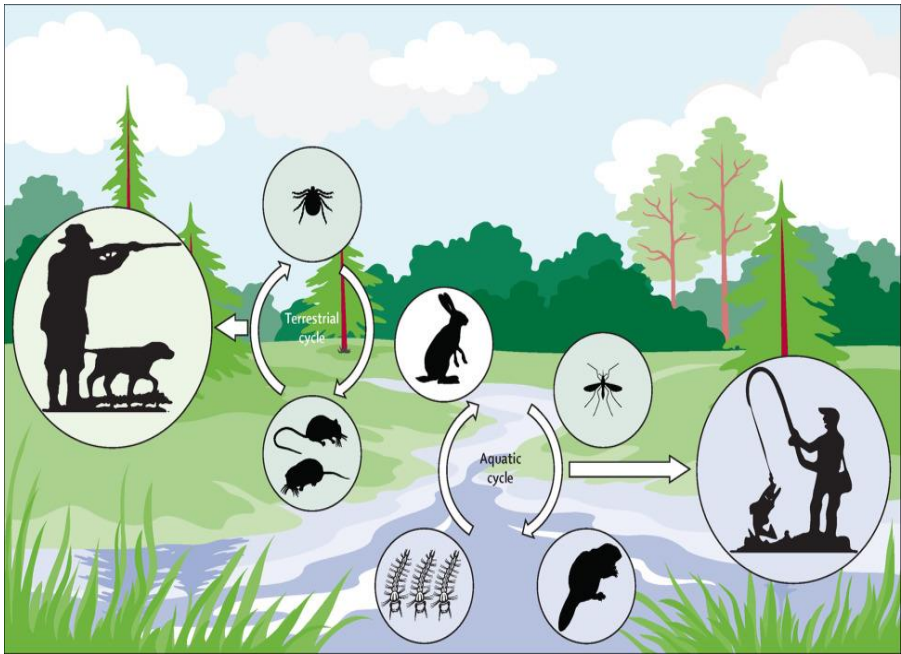


The main epidemiological signs.

The wide spread of the pathogen in nature, the involvement of a large number of warm-blooded animals and arthropods in its circulation, the contamination of various environmental objects (water, food) determine the characteristics of the epidemic process.

There are different types of foci (forest, steppe, meadow-field, name-bog, in the valley of rivers, etc.).

Each type of foci corresponds to its species of animals and bloodsucking arthropods, taking part in the transmission of the pathogen.



Among the diseased adults predominate;
Often the incidence is related to the profession (hunters, fishermen, agricultural workers, etc.).
Men are ill 2-3 times more often than women.
Foci of tularemia occur when migrating infected rodents from their habitats to populated areas, where they come into contact with the synanthropic rodents. Tularemia remains a disease of the countryside, but at the present time there is a steady increase in the incidence of urban population.
Tularemia is recorded throughout the year, but more than 80% of cases occur in the summer and autumn.
In recent years, the incidence of sporadic.

In some years, local transmissible, commercial, agricultural, and water flashes are noted, less often other types of outbreaks.

The transmissible outbreaks are caused by the transmission of the causative agent of the infection by blood-sucking dipterans and occur in the foci of epizootic tularemia among rodents.

Pulmonary outbreaks usually begin in July or June, peak in August and end in September-October;

The increase in the incidence is facilitated by haymaking and harvesting.

The industrial type of outbreaks is usually associated with the capture of the water rat and muskrat. Fishing flashes occur in spring or early summer during the flood period, and their duration depends on the period of harvesting. Infection occurs by contact with animals or skins; The pathogen penetrates through the lesions on the skin, which is why axillary buboes often arise, often without ulcers at the site of implantation.

Water flashes determine the entry of pathogens into open water bodies. The main polluter of water is the water vole, which live along the coast. Diseases usually occur in the summer with a rise in July. Diseases are associated with field work and the use of water for drinking from random ponds, wells, etc.

Agricultural outbreaks occur when inhaling air-dust aerosol when working with straw, hay, grain, fodder, contaminated urine of rodent patients.

Pulmonary, less often abdominal and angino-bubonic forms predominate.

Household type of outbreaks characterizes infection in everyday life (at home, at the estate). Infection is also possible during sweeping the floor, reassembling and drying agricultural products, distributing food to pets, eating contaminated foods.

Infection in humans can occur by one of the following routes:

- **- bite from an arthropod vector (tick or mosquito);**
- **- skin contact with an infected carcass;**
- **- inhalation of the organism (particularly by laboratory workers);**
- **- ingestion of meat contaminated with the bacterium;**
- **- bite from the animal (including pets) that harbor the organism in the oropharynx.**

Pathogenesis.

Gate infections are often microtraumas of the skin.
For the development of the disease when introducing into the skin or aspirating, enough 10-50 viable microorganisms, and with nutritional infection requires more than 108 microbial cells.
The inflammatory process develops on the site of introduction, massive multiplication of microbes occurs, then they penetrate into the regional lymph nodes, causing inflammation. Here, microbes multiply, partially die, releasing endotoxin, which enters the bloodstream and causes common intoxication. When germs get into the blood, hematogenous dissemination occurs in various organs and tissues.
There is a multiple increase in lymph nodes, granulomas can develop in different organs (liver, spleen, lungs).
The granulomatous process is especially pronounced in regional lymph nodes, here necrosis areas are formed. A large amount of granulomas is found in the spleen, liver.
By the cellular composition, tularemia granulomas resemble tuberculosis.
Postponed disease leaves behind a persistent immunity.

The development of various clinical forms of the disease is associated with the mechanism of infection and the entrance gates of infection, which determine the localization of the local process. After penetration of the pathogen, a bubonic form develops through the skin in the form of regional lymphadenitis infection (bubo) in relation to the gates. Possible isolated or combined lesions of various groups of lymph nodes - axillary, inguinal, femoral.

In addition, with secondary hematogenous dissemination of pathogens, secondary buboes can form.

There is soreness, and then an increase in the lymph nodes to the size of a hazelnut or a small chicken egg.

At the same time pain reactions gradually decrease and disappear. The contours of bubo remain distinct, the phenomena of periadenitis are insignificant.

In the dynamics of the disease, buboes slowly (sometimes within a few months) dissolve, swell with the formation of fistula and discharge of creamy pus or sclerosize.

The causative agent of tularemia penetrates through the microtraumas of the skin and through the mucous membranes.

→ In these cases, a skin-bubonic or ocular bubonic form of tularemia occurs (the latter form can develop when a conjunctiva of infected water hits the conjunctiva)

When drinking water or products contaminated by rodents,

→ Intestinal or angino-bubonic forms of tularemia.

Infection can occur by aerogenic (inhalation of infected dust), which leads more often

→ To the development of a pulmonary form of tularemia.

Tularemia can be transmitted by transmission with the bites of various blood-sucking insects

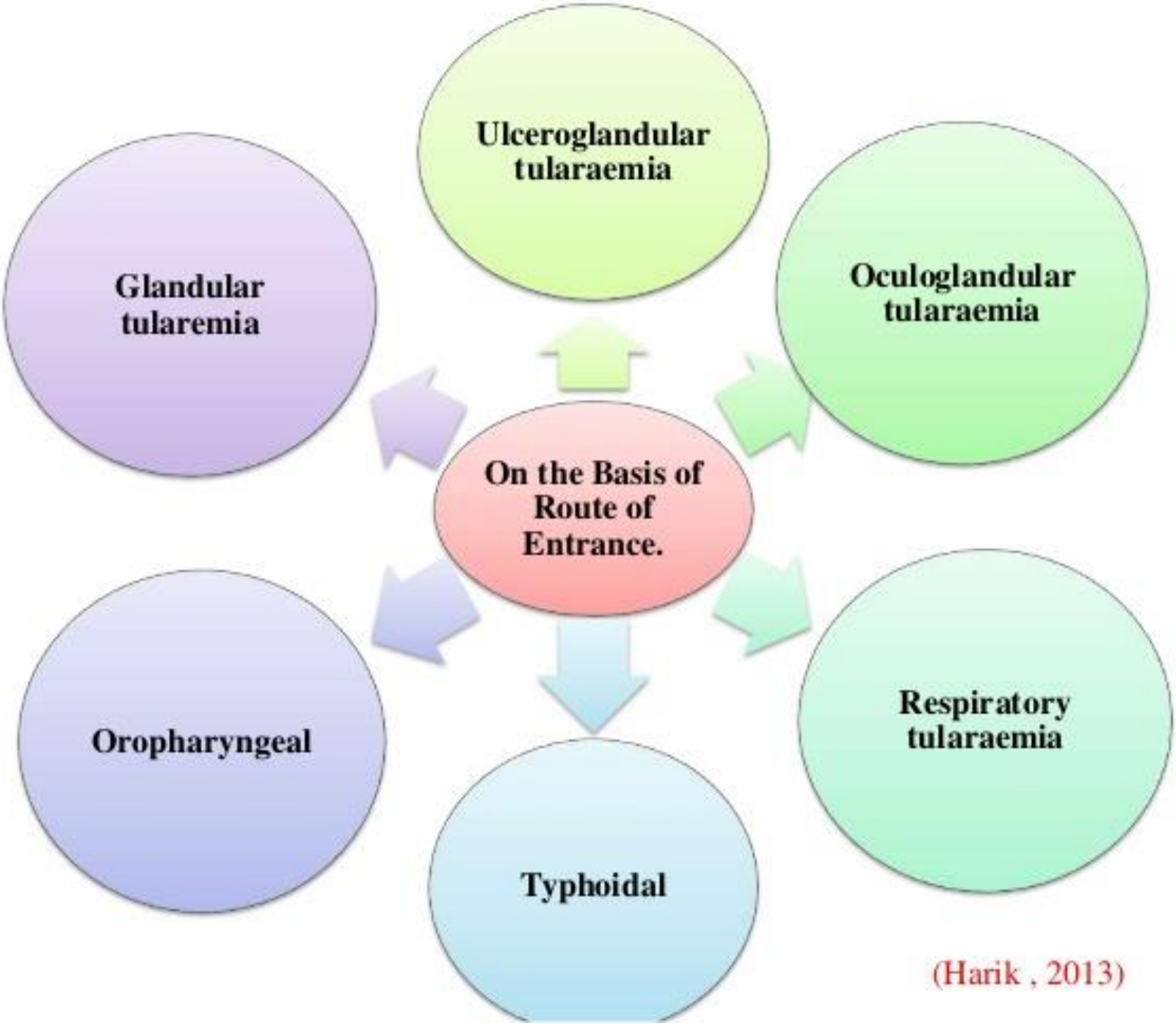
→ There is a dermal-bubonic form of tularemia

Incubation period

Lasts from 1 to 30 days, most often it is 3-7 days.
Signs of the disease, common to all clinical forms, are expressed in an increase in body temperature to 38-40 ° C with the development of other symptoms of intoxication - chills, headache, muscle pain, general weakness, anorexia.
Fever can be remitting (most often), permanent, intermittent, wave-like (in the form of two or three waves).
Duration of fever varies, from 1 week to 2-3 months, most often it lasts 2-3 weeks. When examining patients, there is hyperemia and pastosity of the face, as well as the mucous membrane of the mouth and nasopharynx, injection of sclera, congestion hyperemia. In some cases, there is an exanthema of a different nature: erythematous, maculopapular, roseous, vesicular, or petechial. The pulse is weakened (relative bradycardia), blood pressure is reduced. A few days after the onset of the disease develops hepatolyenal syndrome.

THE CLINICAL MANIFESTATIONS OF TULAREMIA HAVE BEEN DIVIDED INTO 7 FORMS:

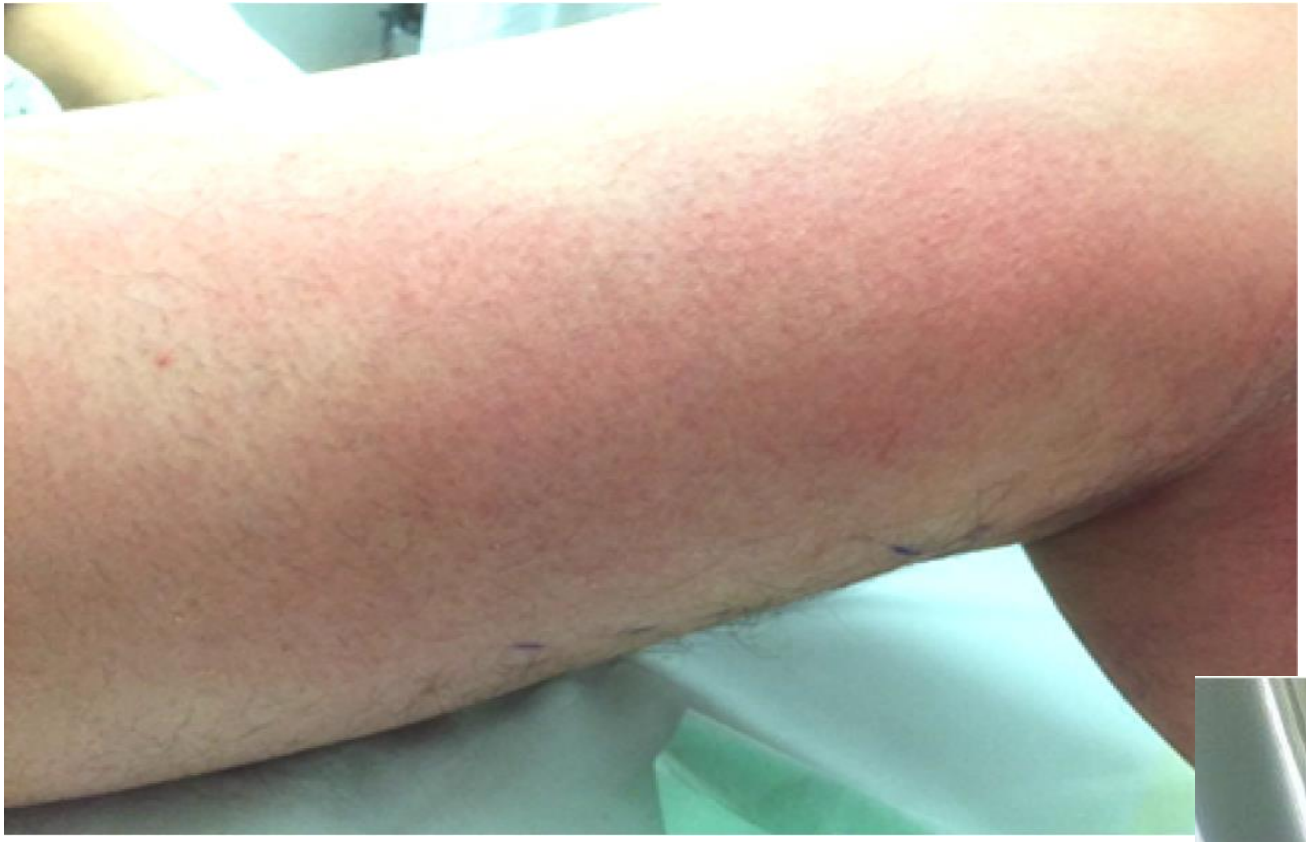
1) ulceroglandular tularemia
2) glandular tularemia
3) oculoglandular tularemia
4) oropharyngeal tularemia,
5) gastrointestinal tularemia
6) pulmonary tularemia,
7) typhoidal tularemia.

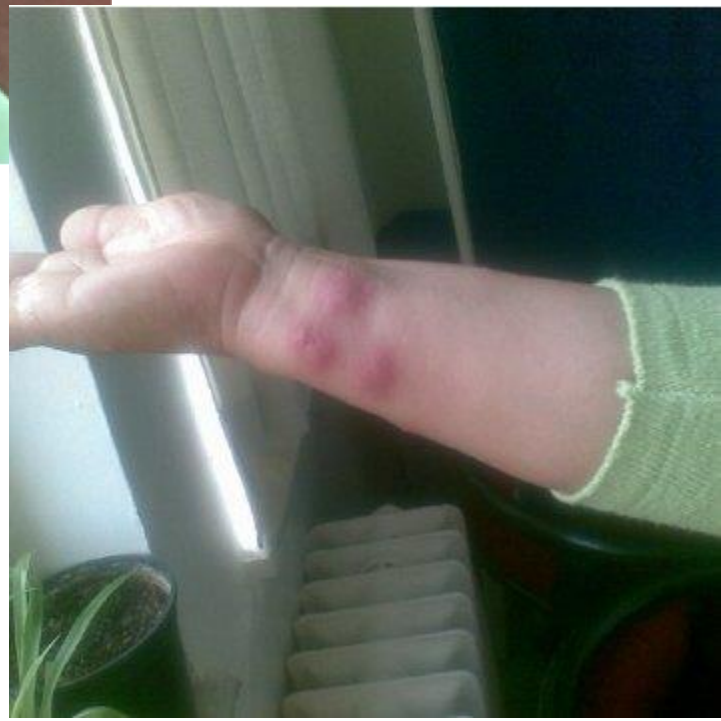

Ulceroglandular tularaemia
Glandular tularemia
Oculoglandular tularaemia
On the Basis of Route of Entrance.
Oropharyngeal
Typhoidal
Respiratory tularaemia

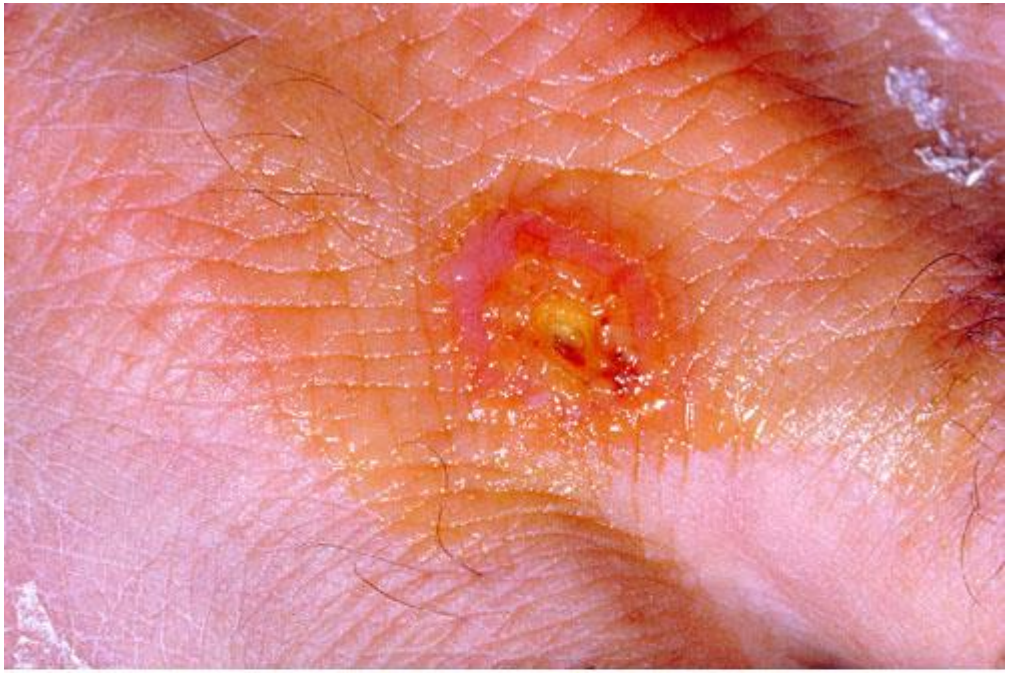
(Harik , 2013)

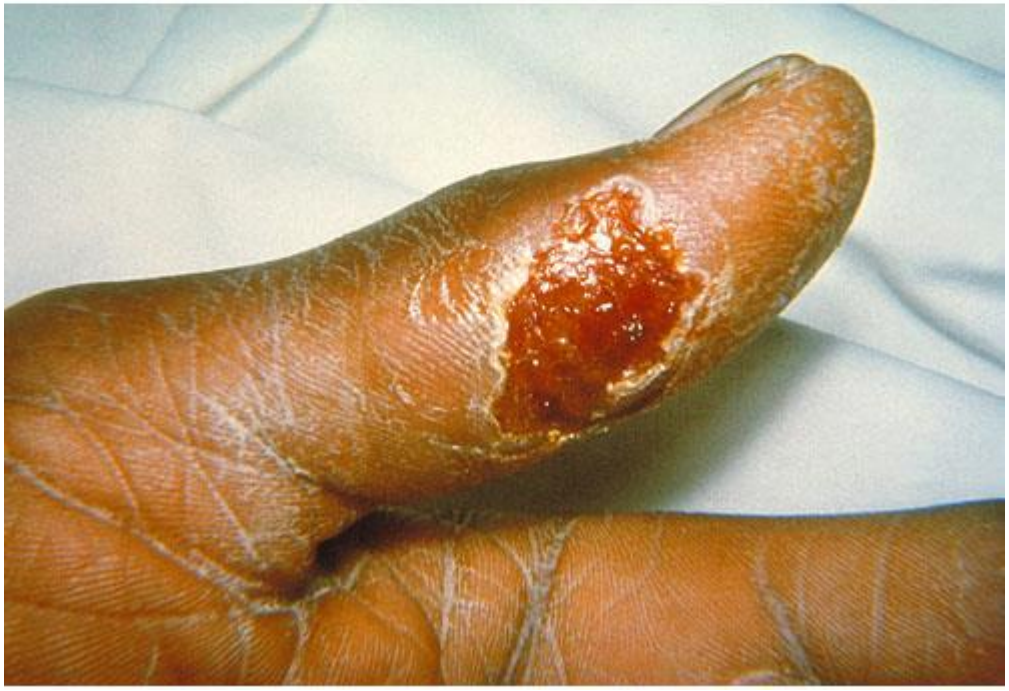
Ulceroglandular & glandular tularemia.

These two forms of tularemia account for ~75–85% of cases. Within 2–5 days (range, 1–10 days) after inoculation into the skin, *F. tularensis* produces an erythematous, tender, or pruritic papule. It evolves over several days into an painful ulcer with sharply demarcated edges and a yellow exudate. The ulcer gradually develops a black base, and simultaneously the regional lymph nodes become tender and severely enlarged. The ulcer is erythematous, indurated, and nonhealing, with a punched-out appearance that lasts 1–3 weeks. The affected lymph nodes may become fluctuant and drain spontaneously, but usually the condition resolves with effective treatment. The predominant form in children involves cervical or posterior auricular lymphadenopathy. In adults, the most common form is inguinal/femoral lymphadenopathy. Glandular tularemia is differentiated from the ulceroglandular form of the disease by the absence of identifiable skin lesion.



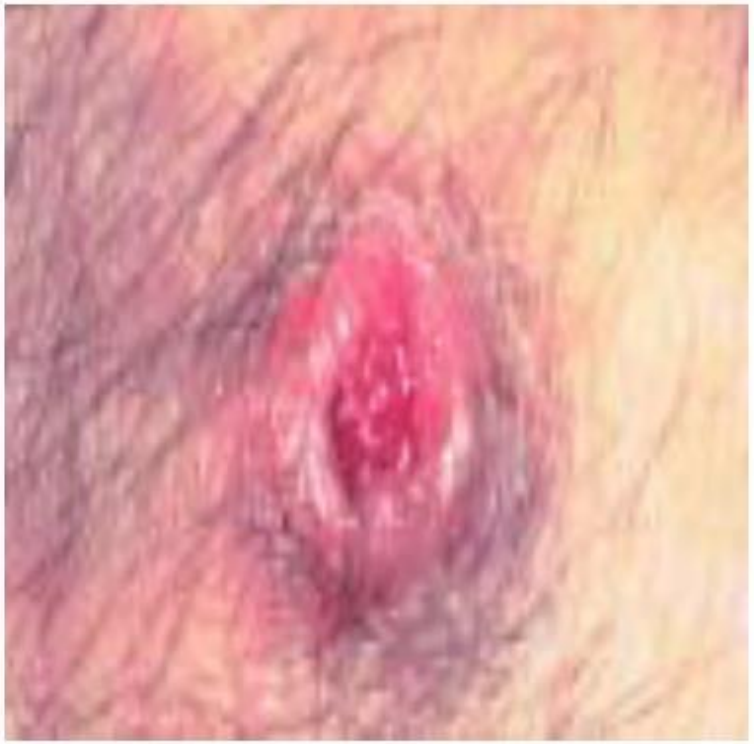


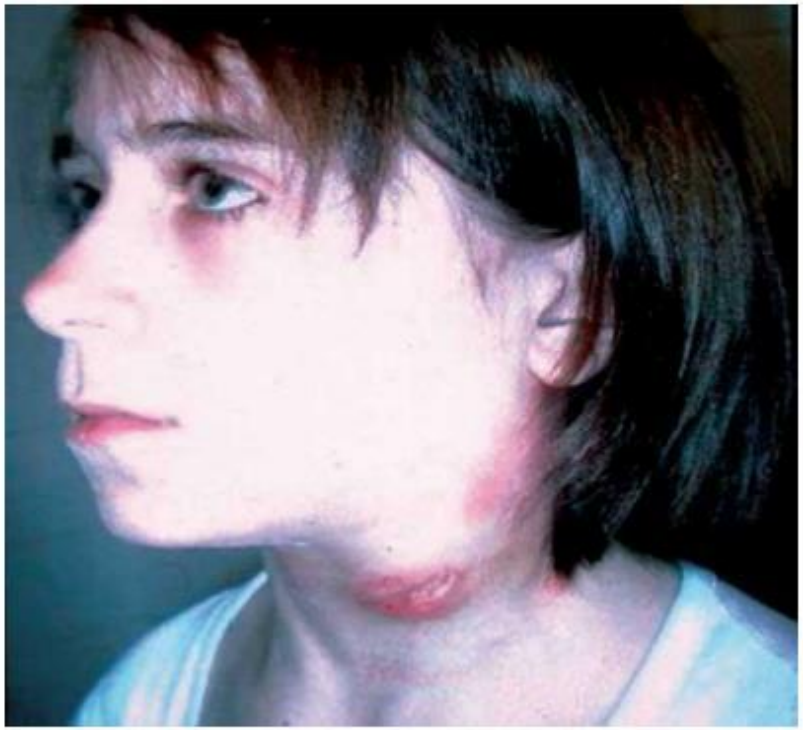


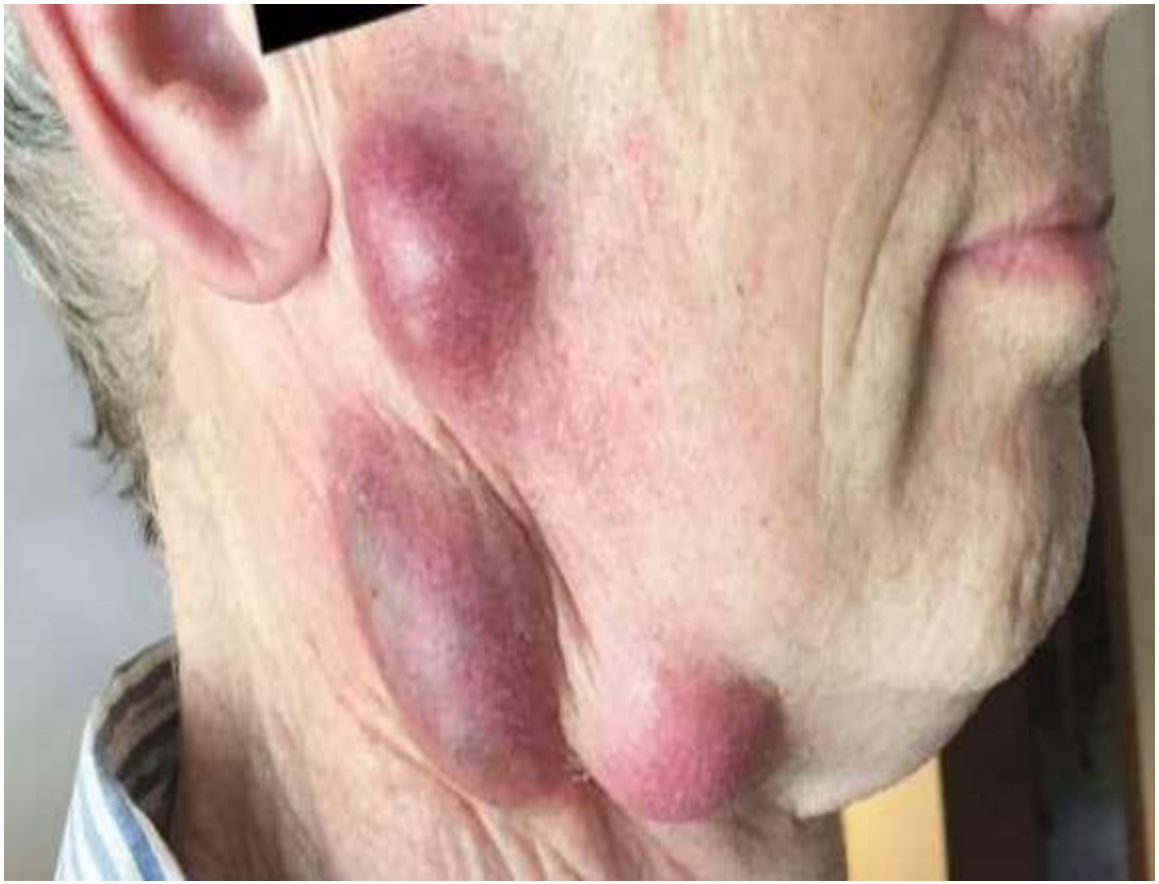


Ulceroglandular tularemia.

Ulceroglandular Tularemia







glandular tularemia

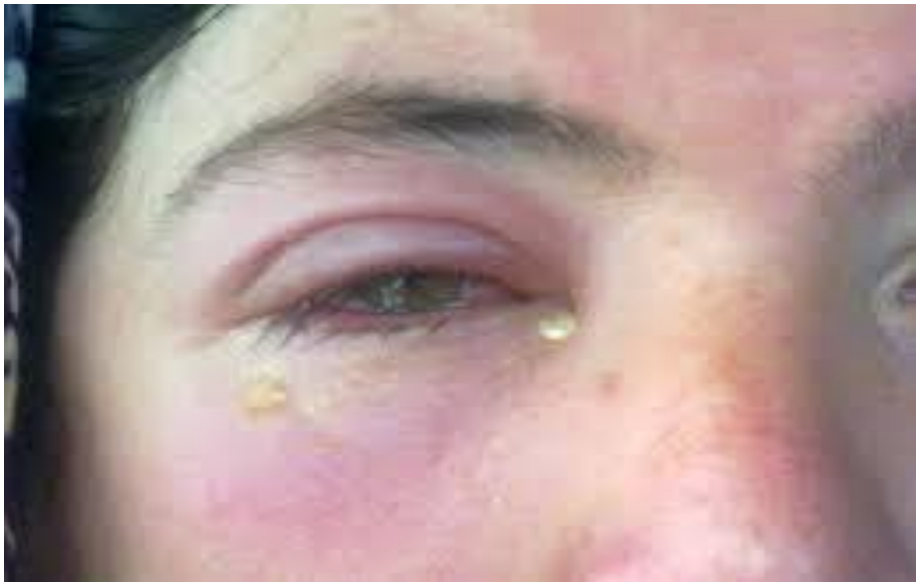
Oculoglandular tularemia.

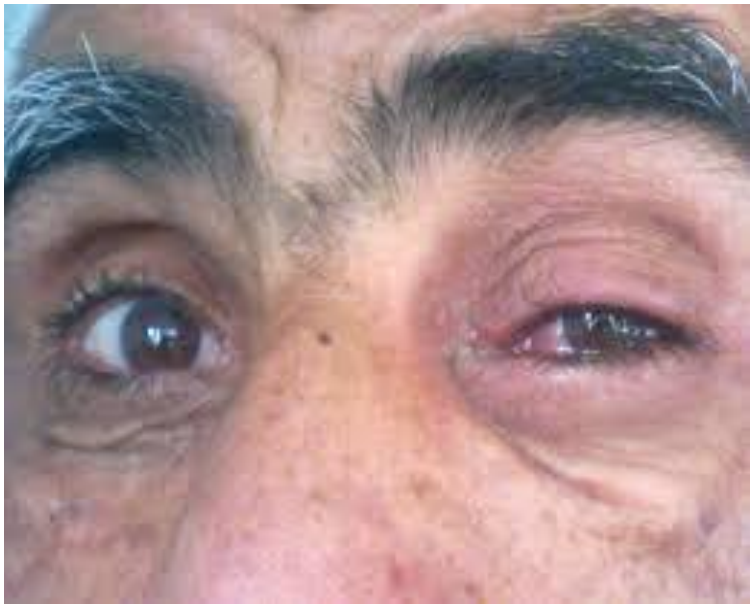
In ~1% of patients, the portal of entry for *F. tularensis* is the conjunctiva. Usually, the organism reaches the conjunctiva through contact with contaminated fingers.

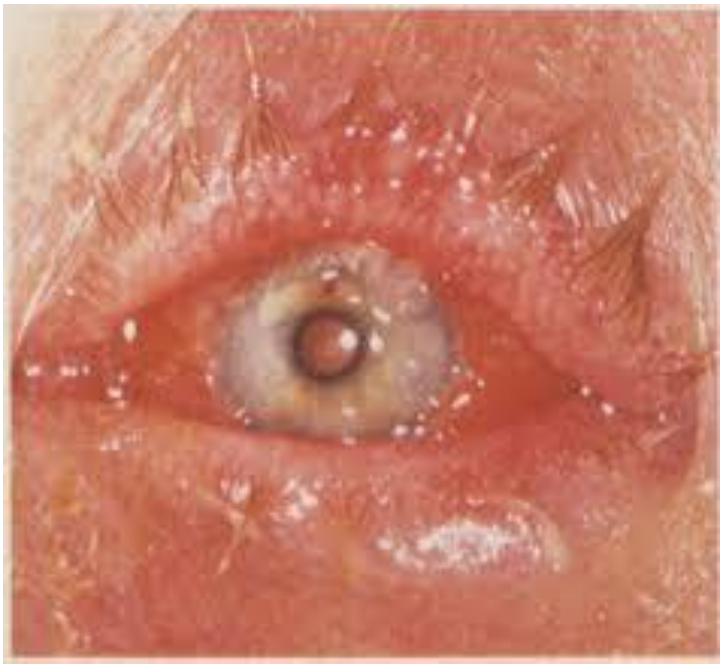
The inflamed conjunctiva is painful, with numerous yellowish nodules and pinpoint ulcers.

Purulent conjunctivitis with regional lymphadenopathy (preauricular, submandibular, or cervical) is evident. Because of debilitating pain, the patient may seek medical attention before regional lymphadenopathy develops.

Corneal perforation may occur.





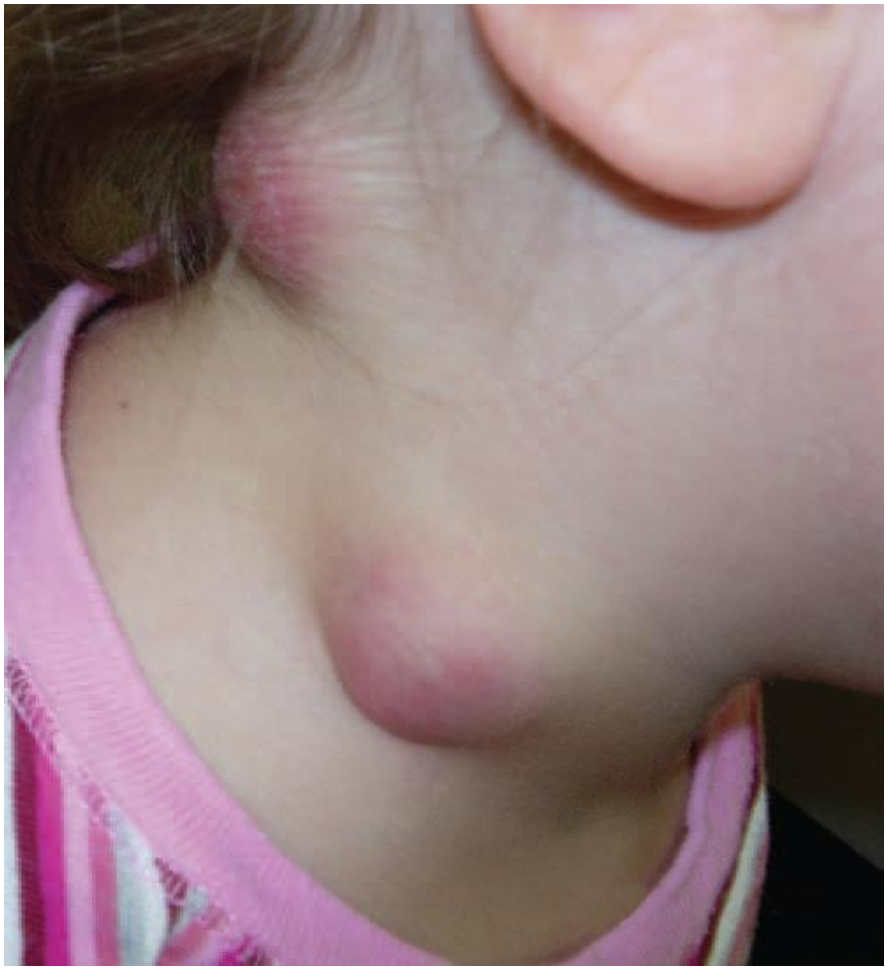


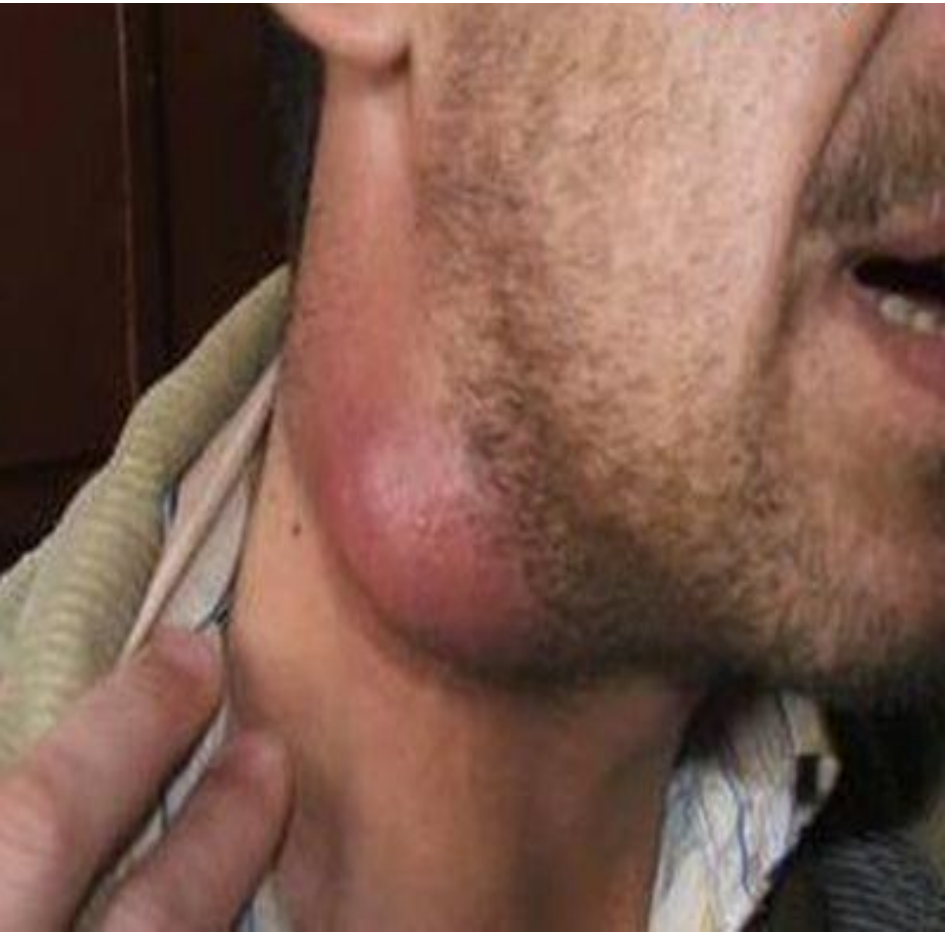
Oropharyngeal & gastrointestinal tularemia.

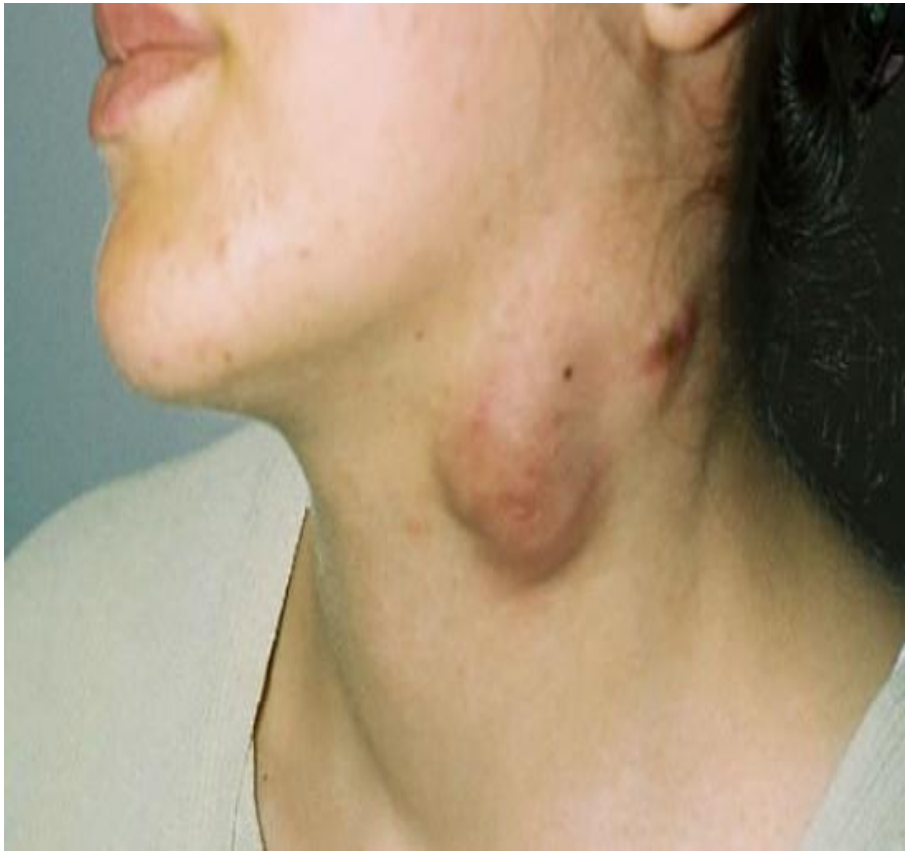
Oral inoculation may result in acute, exudative, or membranous pharyngitis associated with cervical lymphadenopathy or in ulcerative intestinal lesions associated with mesenteric lymphadenopathy, diarrhea, abdominal pain, nausea, vomiting, and gastrointestinal bleeding.

Infected tonsils become enlarged and develop a yellowish-white pseudomembrane, which can be confused with that of diphtheria.

The clinical severity of gastrointestinal tularemia varies from mild, unexplained, persistent diarrhea with no other symptoms to a fulminant, fatal disease.

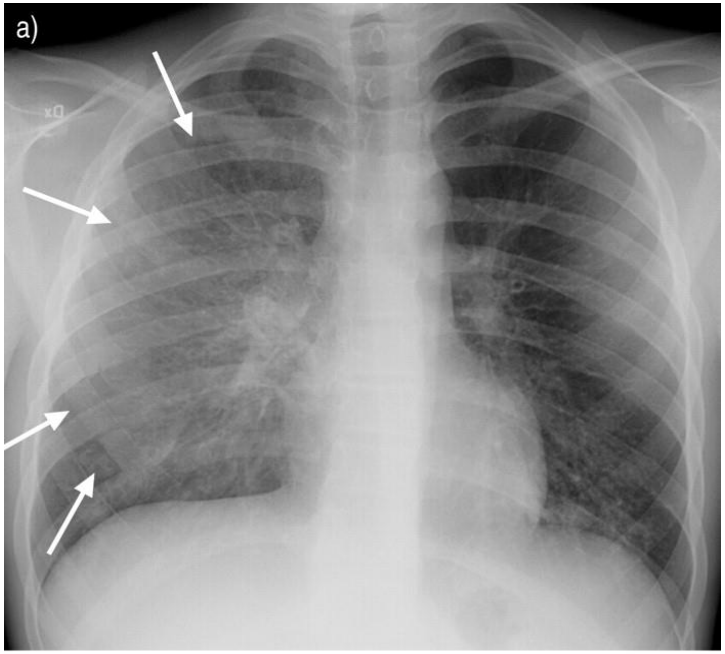






Pulmonary tularemia

Associated with inhalation of the organism or hematogenous spread. Patients with pneumonia usually have a nonproductive cough and may have dyspnea or pleuritic chest pain. Roentgenograms of the chest usually reveal bilateral patchy infiltrates (described as ovoid or lobar densities), lobar parenchymal infiltrates, and cavitary lesions. Pleural effusions may have a predominance of mononuclear leukocytes or polymorphonuclear neutrophils and sometimes red blood cells. Empyema may develop.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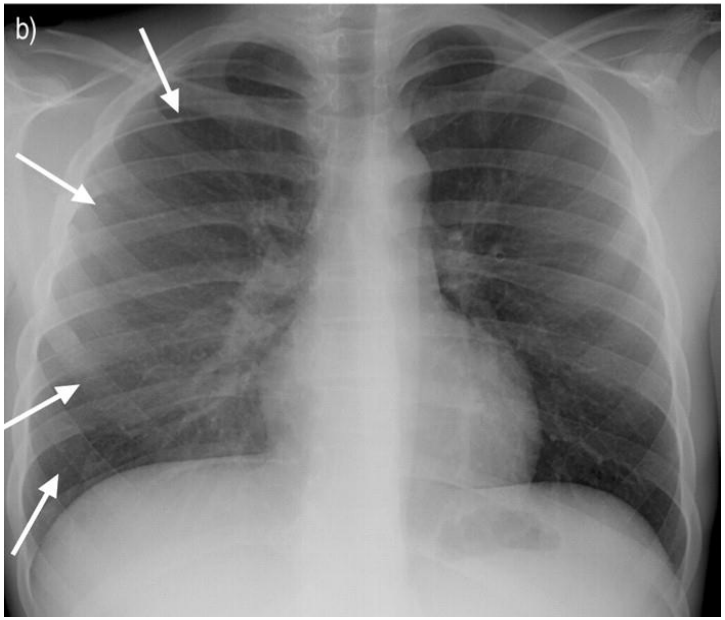
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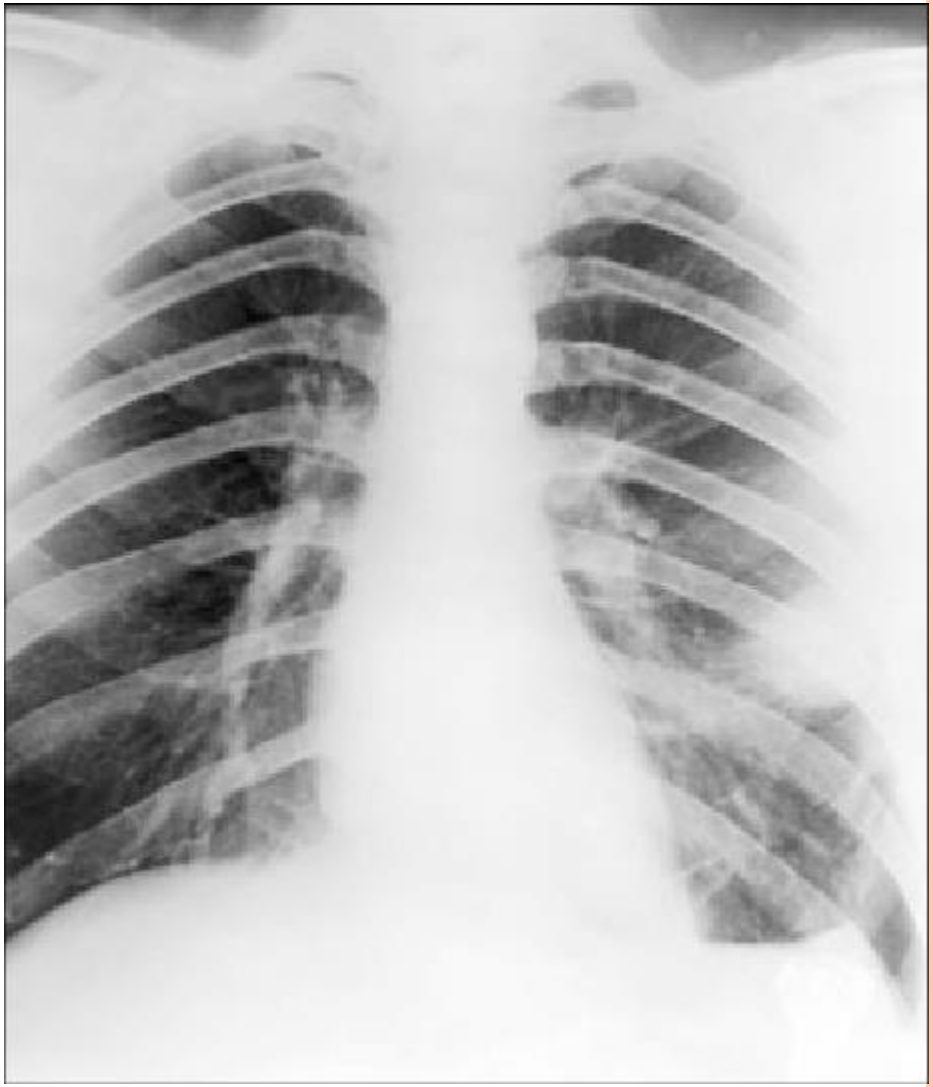


Typhoidal tularemia.

The source of infection in typhoidal tularemia is usually associated with pharyngeal and/or gastrointestinal inoculation or bacteremic disease.

Typhoidal tularemia is usually associated with a huge inoculum or with a preexisting compromising condition. Fever usually develops without apparent skin lesions or lymphadenopathy. In the absence of a history of possible contact with a vector, diagnosis can be extremely difficult. High continuous fevers, signs of endotoxemia, and severe headache are common. The patient may be delirious and may develop prostration and shock. *F. tularensis* infection has been associated with meningitis, pericarditis, hepatitis, peritonitis, endocarditis, osteomyelitis, and sepsis and septic shock with rhabdomyolysis and acute renal failure. In the rare cases of tularemia meningitis, a predominantly lymphocytic response is demonstrated in cerebrospinal fluid.

Complications

In most cases, they develop in a generalized form.

The most common secondary tularemia pneumonia.

Possible infectious-toxic shock.

In rare cases, meningitis and meningoencephalitis, myocarditis, polyarthritis, and others are observed.

Diagnosis.

When patients in endemic areas present with fever, chronic ulcerative skin lesions, and large tender lymph nodes, a diagnosis of tularemia should be made presumptively, and confirmatory diagnostic testing and appropriate therapy should be undertaken.

When the possibility of tularemia is considered in a nonendemic area, an attempt should be made to identify contact with a potential animal vector.

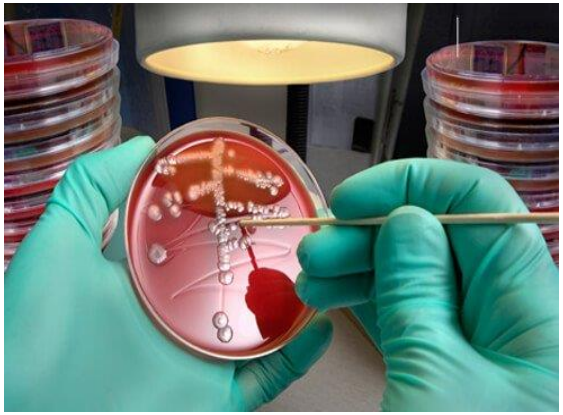
Laboratory diagnostics

In the first days of the disease in the peripheral blood, moderate leukocytosis, a neutrophil shift to the left, an increase in ESR are noted. In the future, leukocytosis can replace leukopenia with lymphocytosis and monocytosis.

In clinical practice, serological methods of research - RA (minimal diagnostic titer 1: 100) and RNGA with increasing antibody titer in the course of the disease are widely used. ELISA on solid-phase carrier is positive from 6-10 days after the disease, diagnostic titer 1: 400;

By sensitivity it is 10-20 times higher than other methods of serological diagnosis of tularemia.
Also, the setting of a skin-allergic test with tularin is common: 0.1 ml of the drug is injected intradermally into the middle third of the forearm from the inside; The reaction result is taken into account after 1-2 days. The sample is highly specific and effective already in the early stages (on the 3-5th day) of the disease.
Its positive result is expressed in the appearance of infiltration, soreness and hyperemia with a diameter of at least 0.5 cm.
It should be taken into account that the sample can also be positive in persons who have recovered from tularemia.

Bacteriological diagnosis of tularemia is of secondary importance, since isolation of the pathogen from blood or other pathological materials is difficult and not always effective. Excretion is possible in the first 7-10 days of the disease, but this requires special media and laboratory animals. Isolation of the pathogen, as well as setting a biological sample with infection of white mice or guinea pigs with punctate buboes, blood of patients, separated by conjunctiva and ulcers are possible only in special laboratories for work with pathogens of especially dangerous infections.



Molecular genetic method: PCR is positive in the initial feverish period of the disease and is a valuable method of early diagnosis of tularemia.

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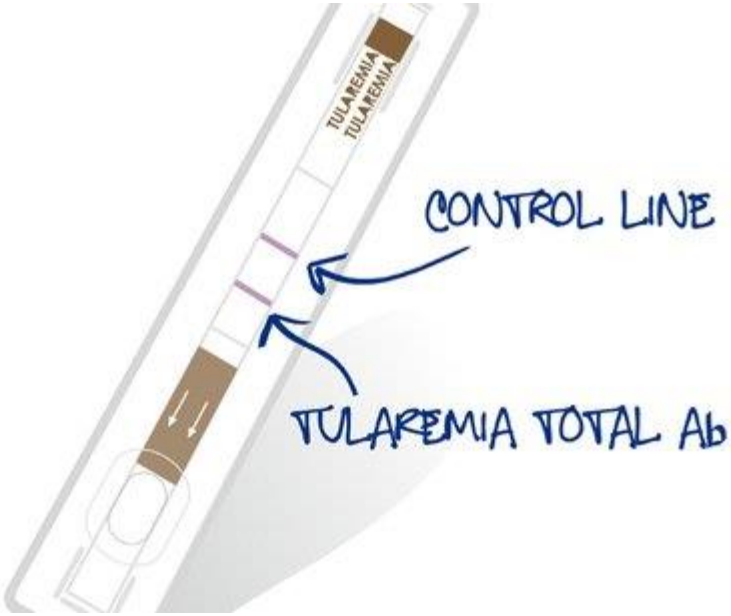
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Differential diagnosis

Tularemia should be distinguished from lymphadenitis of coccal,

- **tuberculosis and other etiology,**
- **lymphogranulomatosis,**
- **pneumonia (with pulmonary form),**
- **lymphosarcoma,**
- **felinosis,**
- **infectious mononucleosis,**
- **ornithosis,**
- **Ku-fever,**
- **in natural foci - from plague.**

Treatment

The drug of first choice for the treatment of all forms of tularemia except meningitis is streptomycin (7.5 to 10 mg/kg bid IM) for 7 to 14 days, although gentamicin (3-5 mg/kg/d IV) is an acceptable substitute.

Fluoroquinolones (ciprofloxacin and moxifloxacin) are the another treatment option for mild to moderate tularemia.

Tetracycline and chloramphenicol are to be used with caution due to the high rate of relapse after treatment with these agents.

Additional treatment includes desintoxication and symptomatic therapy, antihistamines and anti-inflammatory drugs (salicylates), vitamins, cardiovascular drugs.

Surgical therapies are limited to drainage of abscessed lymph nodes and chest tube drainage of empyemas.

For local treatment of buboes and skin ulcers, ointment dressings, compresses, laser irradiation, diathermy are used.

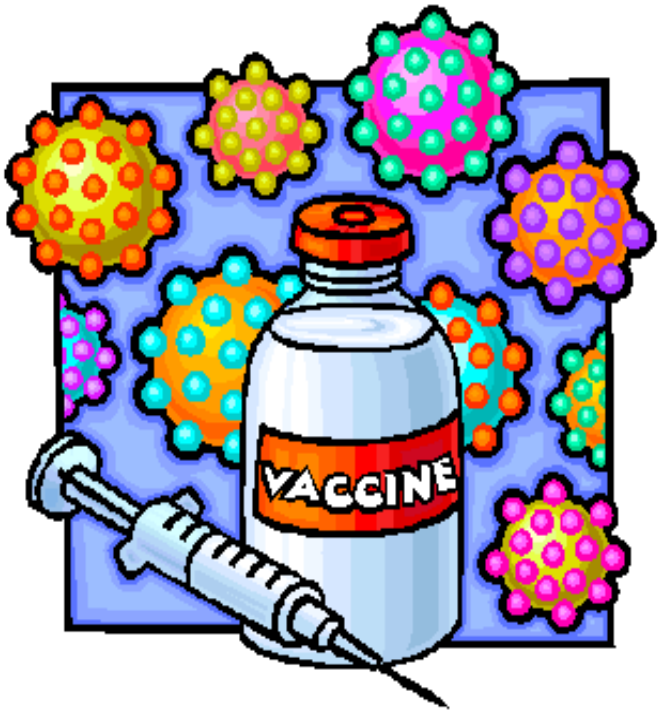
When suppuration of the bubo, it is opened and drained.

Patients are discharged from the hospital after a clinical recovery.

Long-lasting non-absorbable and sclerotized buboes are not a contraindication for discharge.

Prevention.

A live attenuated vaccine is available for people at high risk of infection. It does not provide complete protection but reduces the severity of the disease.
For immunoprophylaxis, a live attenuated vaccine is used. Vaccination ensures the formation of persistent and prolonged immunity in vaccinated (5-7 years and more). Revaccination is carried out after 5 years to contingents subject to routine vaccination.



Gloves, masks, and protective eye covers should be worn when skinning and dressing wild animals and when disposing of dead animals brought home by household pets. Wild game should be cooked thoroughly before ingestion. Wells or other waters that are contaminated by dead animals should not be used.

The most important measure to avoid tick bites in infested areas is wearing clothing that is tight at the wrists and ankles and that covers most of the body. Chemical tick repellants may also be of benefit. Ticks should be removed promptly.

Antibiotic prophylaxis after potential exposures of *unknown risk*, such as tick bites, is not recommended.

Either doxycycline (0.1 g bid) or ciprofloxacin (0.5g bid) given orally for 14 days is recommended for adults with suspected or proven *high-risk* exposure to *F. tularensis*.