Tularemia

Rabbit Fever,
Deerfly Fever,
Meat-Cutter's Disease
Ohara Disease,
Francis Disease

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Importance

Tularemia is a zoonotic bacterial disease with a wide host range. Infections are most prevalent among wild mammals and marsupials, with periodic epizootics in lagomorphs and rodents, but clinical cases also occur in sheep, cats and other domesticated species. A variety of syndromes can be seen, but fatal septicemia is common in some species. In humans, tularemia varies from a localized infection to fulminant, life-threatening pneumonia or septicemia.

Tularemia is mainly seen in the Northern Hemisphere, where it has recently emerged or re-emerged in some areas, including parts of Europe and the Middle East. A few endemic clinical cases have also been recognized in regions where this disease was not thought to exist, such as Australia, South Korea and southern Sudan. In some cases, emergence may be due to increased awareness, surveillance and/or reporting requirements; in others, it has been associated with population explosions of animal reservoir hosts, or with social upheavals such as wars, where sanitation is difficult and infected rodents may contaminate food and water supplies. Occasionally, this disease may even be imported into a country in animals. In 2002, tularemia entered the Czech Republic in a shipment of sick pet prairie dogs from the U.S.

Etiology

Tularemia is caused by *Francisella tularensis* (formerly known as *Pasteurella tularensis*), a Gram negative coccobacillus in the family Francisellaceae and class γ-Proteobacteria. Depending on the author, either three or four subspecies are currently recognized. *F. tularensis* subsp. *tularensis* (also known as type A) and *F. tularensis* subsp. *holarctica* (type B) cause most clinical cases. They are further subdivided into subtypes (A1a, A1b and A2) or biovars (I, II and III/japonica), respectively. These two subspecies and their subtypes/ biovars can differ in factors such as geographic distribution, virulence and antibiotic susceptibility. The other two subspecies, *F. tularensis* subsp. *mediasiatica* and *F. tularensis* subsp. *novicida*, have been recognized in limited geographical regions, are rarely found in people, and seem to be less pathogenic. Some authors do not recognize the latter organism to be a subspecies of *F. tularensis* and call it *F. novicida*. As of 2017, its name has not been formally clarified.

Other species of *Francisella*, such as *F. hispaniensis* and *F. philomiragia*, have also been associated with illnesses in humans and animals. There is relatively little information about these organisms, but they seem to be less virulent than *F. tularensis*, and most (though not all) reported clinical cases occurred in people who had concurrent illnesses or were immunocompromised.

Species Affected

More than 250 species of terrestrial and aquatic animals are known to be susceptible to infection by *F. tularensis* subsp. *tularensis* and/or *F. tularensis* subsp. *holarctica*. Common wild animal hosts include lagomorphs (cottontail rabbits [*Sylvilagus* spp.], various hares and jackrabbits [*Lepus* sp.]), muskrats (*Ondatra zibethicus*), beavers (*Castor canadensis*), and a variety of rodents such as voles, field mice, squirrels and lemmings. These species also develop clinical signs in many cases. Numerous other wild mammals and marsupials can also be infected, and may become ill. In Australia, *F. tularensis* subsp. *holarctica* has been detected in sick or dead ringtail possums (*Pseudocheirus peregrinus*). Among domesticated animals, tularemia occurs in sheep, cats, rabbits, dogs, pigs, horses, ranched mink, pet rodents and other species. Outbreaks have also been seen in captive nonhuman primates. Cattle seem to be relatively resistant to illness, although a few clinical cases have been reported. Infections occur occasionally in birds, reptiles, amphibians, crayfish, mollusks and fish; however, some of these animals might have been contaminated temporarily by *F. tularensis* from their environment (e.g., water).

The reservoir hosts are still uncertain. Wild rodents (e.g., voles) and lagomorphs have been proposed as possible reservoirs for *F. tularensis* subsp. *tularensis* and *F. tularensis* subsp. *holarctica*, and might maintain these organisms during interepidemic periods in some areas. However, lagomorphs and rodents can become severely ill, and might only act as amplifying hosts for organisms acquired from an unknown reservoir.

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Little is known about the susceptibility of animals to the other two subspecies. *F. tularensis* subsp. *mediasiatica* has been detected in hares and Gerbillinae (gerbils and their relatives). *F. tularensis* subsp. *novicida* has not been identified, to date, in naturally infected animals, although experimental infections have been established in mice, guinea pigs and rabbits, and some of these animals became ill.

Zoonotic potential

All four subspecies of *F. tularensis* can affect humans, although illnesses caused by *F. tularensis* subsp. *novicida* and *F. tularensis* subsp. *mediasiatica* seem to be uncommon.

Geographic Distribution

Tularemia mainly seems to occur in the Northern Hemisphere, with most reports originating from North America, Europe, Asia, the Middle East and northern Africa. Within an endemic region, clinical cases are more common in some areas (e.g., south-central U.S. states, Scandinavian countries) than others. Infections have also been documented in animals and humans in Australia, and an endemic case was recently reported in a person in southern Sudan.

The four subspecies of *F. tularensis* have different geographic distributions. *F. tularensis* subsp. *tularensis* occurs almost exclusively in North America, with only a few reports of its detection in Europe. Different subtypes of this organism predominate in different parts of North America. *F. tularensis* subsp. *holarctica* is widely distributed in the Northern Hemisphere, including North America, and also occurs in Australia. *F. tularensis* subsp. *mediasiatica* has been found in a limited area of Central Asia, and *F. tularensis* subsp. *novicida* has been reported from North America and Thailand. Two organisms isolated from humans in Spain and Australia, which were originally identified as *F. tularensis* subsp. *novicida*, have been reclassified as *F. hispaniensis*. An organism found in Sudan was identified as *F. tularensis*, and its subspecies is not known.

Transmission

F. tularensis subsp. tularensis and F. tularensis subsp. holarctica

F. tularensis can be acquired by ingestion, inhalation or contamination of mucous membranes and broken skin, or from an arthropod vector. Relatively little is known about the presence of this organism in secretions or excretions; however, it has been detected in the urine and/or feces of several species of experimentally infected voles. Clinical cases are often linked to contact with tissues or blood from infected animals. People and animals can be infected by eating undercooked animal tissues, or other foods that have been contaminated by infected carcasses or excretions. Cannibalism seemed to be the primary route of transmission during an outbreak in captive prairie dogs. Hunting or skinning animals, and other unprotected contact with tissues (including meat during food preparation and tissue samples during necropsies) are important routes of exposure for people. People have also been infected when they handled live animals or were licked, bitten or scratched by them. Some of these animals were not ill, and their mouths or claws may have been colonized temporarily after contact with an infected rodent or other host. Aquatic animals may develop tularemia after being immersed in contaminated water, and some human cases have been linked to drinking contaminated water, including well water, or near-drowning events. Respiratory infections sometimes occur in farmers exposed through activities such as piling hay. Similar cases have also been reported after mowing lawns, possibly from organisms that were aerosolized by running over an animal carcass. Person-to-person transmission has not been reported.

Transmission from the environment is facilitated by the prolonged survival of *F. tularensis*. This organism was reported to remain viable for weeks to months in some sources, including the carcasses and hides of infected animals, grain dust, straw, water and soil. Live bacteria were found after 3 years in rabbit meat stored at -15°C. One study found that both *F. tularensis* subsp. *tularensis* and *F. tularensis* subsp. *holarctica* survived longer in brackish water (2-3 weeks or more) than fresh water, where survival was relatively brief. However, organisms in fresh water might be maintained longer within aquatic protozoans.

Arthropod vectors are also important in transmission. Various species of ixodid ticks are known to be biological vectors. In addition to being linked to sporadic clinical cases, ticks are thought to be important in causing outbreaks among sheep. Transstadial transmission has been demonstrated in some tick species, but the possibility of transovarial transmission is controversial. Biting flies in the family Tabanidae (e.g., the deer fly, *Chrysops discalis*) and mosquitoes can act as mechanical vectors. Individual flies have been shown to carry the organism for two weeks. Transstadial transmission has been demonstrated in mosquitoes, which can acquire the organism as larvae in aquatic environments and remain infected as adults. *F. tularensis* has also been found in other arthropods, although their role in transmission is often speculative. *F. tularensis* subsp. *holarctica* was isolated from mites (family Gamasidae) collected from rodents in Europe, and mites could transmit this organism between rodents in the laboratory. Ceratopogonids (biting midges) and Simulidae (blackflies) have also been proposed as potential vectors. Fleas can remain infected for weeks, but are thought to be of little importance because they do not transmit the organism readily between animals in the laboratory. Fruit flies (*Drosophila melanogaster*) have been infected in the laboratory, and bedbugs were reported to harbor the organism for 4.5 months.

F. tularensis subsp. novicida and F. tularensis subsp. mediasiatica

Little is known about how these two subspecies are transmitted. *F. tularensis* subsp. *novicida* has been found in salt or brackish water and soil. Some human infections with this organism were linked to immersion in water, and three cases in a prison were most likely associated with ingesting contaminated ice.

Disinfection

F. tularensis can be killed by variety of disinfectants including 1% hypochlorite, 70% ethanol, glutaraldehyde and formaldehyde. It can also be inactivated by moist heat (121°C/ 250°F for at least 15 min) and dry heat (160-170°C/ 320-338°F for at least 1 hour).

In drinking water, one study reported that the inactivation of *F. tularensis* by routine concentrations of free available chlorine (0.5mg/l) depended on the water's temperature and pH. Inactivation was most efficient at 25°C, pH 7, with the concentration of some strains decreasing 10,000-fold in a minute, and slowest at 5°C, pH 8, where this level of inactivation took up to 1.7 hrs.

Infections in Animals

Incubation Period

The incubation period in animals is estimated to range from one to 10 days.

Clinical Signs

The full spectrum of clinical signs is not known in animals, but syndromes corresponding to the typhoidal, respiratory, ulceroglandular and oropharyngeal forms of humans have all been reported. Highly susceptible species, such as rabbits and rodents, often develop septicemia, but asymptomatic or mild infections also occur, especially in resistant species such as dogs and cattle.

In cats, tularemia often begins acutely, with fever, regional or generalized lymphadenopathy, and general signs of illness, such as lethargy and anorexia. The submandibular lymph nodes are often affected, presumably because most cats are infected via prey. Affected lymph nodes may suppurate and drain. Oral lesions including white patches or ulcers may also be found. Other signs reported in some cases include icterus, hepatomegaly, splenomegaly, weight loss, vomiting, diarrhea and signs of pneumonia. The clinical signs in cats are often severe, and they can be life-threatening if not treated early. However, milder syndromes are possible. For instance, one cat had a chronic draining cutaneous lesion and swelling of the mandibular lymph nodes, but no systemic signs, for about a year before tularemia was diagnosed.

Dogs seem to be relatively resistant to tularemia and may recover spontaneously. Clinical signs that have been reported in this species include anorexia, depression, mild fever, lymphadenopathy (which may be mild), draining abscesses, vomiting, evidence of abdominal pain, and mucoid ocular discharge or conjunctivitis. Experimentally infected dogs that were fed *F. tularensis* developed a self-limited illness with fever and mucopurulent discharge from the nose and eyes. Dogs inoculated intradermally had pustules at the inoculation site and regional lymphadenopathy.

Outbreaks in sheep are usually characterized by late term abortions in ewes, and illnesses and deaths among lambs. Fever, listlessness, regional lymphadenopathy and diarrhea may be seen. Systemic signs are possible but uncommon in adult sheep. Although serological evidence suggests that infections may be fairly common in cattle, a specific syndrome has not been described, and many cases may be asymptomatic. Tularemia has been diagnosed rarely in sick calves.

Captive nonhuman primates may have nonspecific, gastrointestinal and/or respiratory signs similar to those in other species. Some cases are severe and rapidly fatal, and animals may die acutely with few or no clinical signs. However, milder febrile illnesses have also been reported, and some animals seroconvert without any apparent illness.

Signs of septicemia and general malaise may be observed in some wild mammals, domesticated rabbits and pet rodents, but many of these animals are found dead. Both acute septicemia and chronic infections have been reported in wild hares. Cottontail rabbits (*Sylvilagus* spp.) inoculated with *F. tularensis* subsp. *tularensis* developed a severe, disseminated, fatal febrile illness, but most cottontails inoculated with *F. tularensis* subsp. *holarctica* had a mild fever with or without lethargy, and recovered.

Post Mortem Lesions

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Animals with acute tularemia are often in good body condition, but they may also be dehydrated, thin or emaciated. Oral lesions may be detected in some animals infected by ingestion. The liver, spleen and lymph nodes are frequently enlarged, and affected lymph nodes may contain areas of caseous necrosis. Congestion, edema, areas of consolidation, and fibrinous pneumonia or pleuritis may be found in the lungs. Miliary, grayish-white, white or light yellow necrotic foci are often noted in the liver, spleen, bone marrow, lungs and/or lymph nodes. Some of these foci may be barely visible. In rabbits, the pale necrotic foci on a dark, congested liver and spleen have been compared to the Milky Way. Ulcerative enteritis, associated with necrosis of Peyer's patches, can also be seen, and icterus occurs in some cats. Acute necrotizing enteritis or hepatitis were the most common lesions in wild ringtail possums. Occasionally, wild animals infected with *F. tularensis* (e.g., grey squirrels [(*Sciurus griseus*], a stone marten [*Martes foina*]) have had no lesions characteristic of tularemia.

More resistant species, or animals infected with less virulent organisms, may have chronic granulomas that resemble tuberculosis lesions, especially in the spleen, liver, kidneys, lungs and pericardium.

Diagnostic Tests

F. tularensis, its nucleic acids and antigens may be found in various clinical samples including exudates, blood and tissues such as the liver, spleen, enlarged lymph nodes, kidney, lungs and bone marrow. Impression smears may reveal small Gram negative coccobacilli inside cells and scattered among tissue debris. *F. tularensis* is very small (0.2–0.7 µm) and easy to miss, it stains faintly with conventional stains such as Gram stain, and it can look like stain precipitates. Immunofluorescence can help reveal the organism in an impression smear.

PCR assays can detect *F. tularensis* nucleic acids in clinical samples, and antigens can be found by immunostaining or ELISAs. Some PCR tests can identify the subspecies. Cases can also be diagnosed by isolating *F. tularensis*, but culture requires biosafety level 3 (BSL-3) facilities, and it is only available in a limited number of laboratories. *F. tularensis* subsp. *novicida* can be isolated on standard media such as blood agar. However, *F. tularensis* subsp. *tularensis and F. tularensis* subsp. *holarctica* are fastidious and require specialized media containing thiol compounds (e.g., cysteine), such as cysteine heart agar with 9% chocolatized blood (CHAB), buffered charcoal yeast extract (BYCE), McCoy and Chapin medium or modified Thayer/Martin agar. An antibiotic supplemented CHAB medium (CHAB-A) can be helpful with contaminated samples. *F. tularensis* subsp. *tularensis and F. tularensis* subsp. *holarctica* in tissue samples may form colonies on sheep blood agar, but they will not grow well on this medium after subculture. Colonies can be identified with PCR, biochemical tests and assays to detect antigens. Culture and identification of the organism can take from 2 days to more than 2 weeks. Animal inoculation (e.g., mouse) can also be used for isolation, however, this is likely to be done only in exceptional circumstances.

Subtypes of *F. tularensis* can be distinguished by some PCR tests and other genetic methods, as well as by certain biochemical assays (e.g., the ability to ferment glycerol). Other molecular techniques such as restriction fragment linked polymorphism (RFLP) Southern blot, pulsed-field gel electrophoresis (PFGE) and multi-locus variable number tandem repeat assays (MLVA) can be used to identify strains for epidemiological purposes.

Serology is occasionally useful in animals. Species sensitive to tularemia typically die before specific antibodies develop; however, significant titers may be found in more resistant animals such as sheep, cattle, pigs and dogs, or in animals infected by less pathogenic strains. Serological tests include tube or slide agglutination, microagglutination and ELISA. A rising titer should be seen. Cross-reactions may occur with other bacteria such as *Yersinia* spp., *Brucella* spp. and *Legionella* spp.

Treatment

F. tularensis is susceptible to some classes of antibiotics such as tetracyclines, fluoroquinolones and amino-glycosides. Supportive therapy may also be required.

Control

Disease reporting

Veterinarians who encounter or suspect tularemia should follow their national and/or local guidelines for disease reporting. This disease is reportable in some U.S. states.

Prevention

Housing susceptible animals indoors is expected to be helpful. Absolute prevention of tularemia is difficult in animals that spend time outside, due to the numerous sources of the organism. Arthropod control programs, such as tick control programs in livestock, may reduce the risk of vector-borne infections. Measures to prevent contact with susceptible wild and animals (e.g., rodent infestations) and potentially contaminated waters (e.g., lakes, streams) reduce the risks from these sources. Animal feed should be protected from wild rodents and other wild animals. Cats and dogs should not be allowed to hunt where tularemia is endemic.

Morbidity and Mortality

Tularemia is relatively common and highly fatal in some species of wild animals. In particular, epizootics occur regularly in lagomorphs and rodents. Epizootics were also common, at one time, among range sheep in Idaho, Montana and Wyoming, and occasional outbreaks can still occur. Cases in sheep may follow epizootics among lagomorphs or rodents, and infections appear to be acquired via ticks. Adult sheep mainly seem to have reproductive signs, with abortion rates that can reach 50%. Mortality rates as high as 10-15% may be seen in untreated lambs, but adult sheep do not usually become ill.

Clinical cases also seem to be relatively common in cats, which are probably exposed when hunting rodents. Sick cats often have severe clinical signs, and these animals frequently die if they are not treated promptly. However, milder cases are reported occasionally, and some cats with no history of disease are seropositive. Outbreaks have also been seen in captive prairie dogs, ranched mink and nonhuman primates. During some outbreaks in primates, clinical cases occurred primarily in young animals. Some of these cases were severe, but other individuals had relatively mild signs and were treated successfully with antibiotics. Dogs, coyotes, cattle and some other species seem to be relatively resistant to tularemia, and mostly seem to have milder cases or subclinical infections.

There is little information about the effects of *F. tularensis* subsp. *novicida* on animals. Based on experiments in rodents and rabbits, this organism seems to cause milder illnesses than *F.* subsp. *tularensis* subsp. *tularensis*, but high doses of the organism can result in fatal illness.

Infections in Humans

Incubation Period

The incubation period in humans is estimated to be 2-20 days; most often, clinical signs appear in approximately 3-5 days.

Clinical Signs

F. tularensis subsp. tularensis and F. tularensis subsp. holarctica

Six forms of tularemia are seen in humans: ulceroglandular, glandular, oculoglandular, oropharyngeal, respiratory and typhoidal.

Ulceroglandular tularemia, the most common form, occurs after exposure via broken skin or mucous membranes. The initial symptoms are nonspecific and flu-like, with signs such as fever, chills, headache, body aches and malaise. An inflamed papule usually develops where the bacteria entered the body, then becomes a pustule that ulcerates. In some cases, this lesion may heal by the time the patient seeks medical care; in others, it persists. Unusual cases with a vesicular skin rash have also been documented. These vesicles were reported to contain clear fluid that becomes turbid with time. Vesicles may also be found around an ulcerated eschar. The regional lymph nodes become enlarged and painful in ulceroglandular tularemia, and may suppurate and drain profusely. Occasional cases with lymph node enlargement, but no apparent signs of systemic illness, have been described. Glandular tularemia is identical to the ulceroglandular form, but there is no lesion to indicate where the organism might have entered the body.

Inoculation of the conjunctiva, often by touching the eye with contaminated fingers, results in oculoglandular tularemia. Most cases are unilateral. Oculoglandular tularemia is characterized by painful, purulent conjunctivitis with preauricular and/or cervical lymphadenopathy. In some cases, there may be periorbital edema and multiple small nodules or ulcerations on the conjunctiva. Corneal perforation and iris prolapse are possible complications. Unilateral (posterior) uveitis has also been reported, though rarely, in cases of tularemia.

Oropharyngeal tularemia can be seen after ingesting *F. tularensis*. In addition to nonspecific signs such as fever malaise and local lymphadenopathy, these patients often develop exudative stomatitis and/or pharyngitis with pustules and ulcers. In many cases, the lymph nodes are visibly enlarged on only one side of the neck. In some cases, the tonsils may also be inflamed. Gastrointestinal signs such as abdominal pain from mesenteric lymphadenopathy, as well as vomiting, diarrhea and gastrointestinal bleeding, are also reported occasionally after ingestion.

Respiratory (pneumonic) tularemia occurs after inhalation of organisms, or hematogenous spread from another site. The symptoms vary in severity, but are generally milder when they are caused by *F. tularensis* subsp. *holarctica*. Sometimes, the only signs of respiratory tularemia are coughing, decreased breath sounds and substernal discomfort. In other cases, there may also be a high fever, chills, malaise, chest pain and dyspnea. Severely affected patients may be weak and, in some cases, delirious. Respiratory involvement has also been reported in patients with systemic signs such as fever (which may be intermittent in chronic cases) and generalized illness, but without symptoms suggestive of respiratory disease. Unless treated promptly, severe respiratory tularemia is often fatal.

Typhoidal tularemia is the term used for systemic infections without an obvious route of exposure. These cases are generally severe. Most are probably the result of inhalation, but this form can also develop after skin inoculation or ingestion. There may be nonspecific signs such as high fever, prostration, headache, nausea, vomiting, diarrhea and weight loss, but lymphadenopathy is usually absent. Some patients become extremely weak and develop recurring chills and drenching sweats. A nonspecific rash may also be seen. Pneumonia also occurs frequently in the typhoidal form, and can be severe.

Diverse complications, some of which seem to be very rare, have been described in cases of tularemia. They include meningitis, encephalitis, endocarditis, pericarditis, aortitis (in a preexisting aortic aneurysm), osteomyelitis, kidney failure, hepatitis and disseminated intravascular coagulation. Abortions or premature delivery occurred in a few pregnant women, although a causative role was not entirely clear. Some pregnant women treated with antibiotics delivered healthy babies. People who have recovered from tularemia can develop localized papules without generalization of the lesions, if they are later exposed to large amounts of the bacterium.

F. tularensis subsp. novicida

Few clinical cases caused by *F. tularensis* subsp. *novicida* have been described to date. One young, healthy person presented with an illness that resembled the ulceroglandular or glandular form, with regional lymphadenopathy and no other symptoms. Another case, in a 15-year-old, was characterized as a reactive lymph node, with a history of swelling on alternating sides of the face and neck for 2-3 weeks, but no fever. This syndrome had been preceded 6 months earlier by a flu-like illness, with intermittent malaise, myalgia, diffuse abdominal pain, nausea, vomiting and diarrhea, with pleural effusion and prominent mesenteric lymph nodes. Whether these earlier signs were related to the lymphadenopathy is unclear.

The remaining cases occurred in people who had concurrent medical conditions (e.g., diabetes) or were immunosuppressed. An older man in poor nutritional condition, with a history of alcoholism, developed a febrile illness that resembled typhoidal tularemia, with dizziness, nausea, vomiting and bacteremia. In another case, *F. tularensis* subsp. *novicida* was isolated from a patient who developed a fever soon after a severe neck injury in a surfing accident. Other cases were described as bacterial peritonitis, pyomyositis of the thigh, and bacteremia. *F. tularensis* subsp. *novicida* was also detected in a woman undergoing chemotherapy for ovarian cancer, who developed a fever and intestinal hemorrhage with melena; however, her clinical signs could also have been caused by the chemotherapy.

Diagnostic Tests

In humans, tularemia is often diagnosed by serology. Commonly used serological tests include tube agglutination, microagglutination and ELISAs. An indirect immunofluorescent assay (IFA) has also been employed by some laboratories. Screening by ELISA, with confirmation by immunoblot, is recommended by some authors. Significant, detectable titers usually appear 10-20 days after infection. A single high antibody titer can be sufficient to

begin treatment as a presumptive case, with a second titer collected for definitive confirmation during convalescence. Cross–reactions can occur with *Brucella* spp., *Legionella* sp., *Proteus* OX19, and *Yersinia* spp., usually at low titers.

Tularemia can also be diagnosed by detecting *F. tularensis* nucleic acids by PCR, or antigens with antigen detection tests (e.g., immunohistochemistry), or by isolating the organism from blood, affected tissues and exudates, as in animals. Sputum, pharyngeal or conjunctival exudates, samples from cutaneous ulcers or, lymph nodes, and gastric washings are among the specimens that have been used for diagnosis in humans. Histopathology can also be helpful.

Treatment

Tularemia is treated with antibiotics effective against this organism. Early treatment is more effective and helps avoid complications such as suppuration of the lymph nodes. Suppurated lymph nodes may occasionally need to be removed.

Prevention

Methods to reduce the risk of tularemia include avoiding bites from arthropods, contaminated food and water, and direct contact with infected animals or their tissues. Protective clothing (e.g., long pants, shirts with long sleeves, mesh head nets), insect repellents and/or other measures can help prevent bites from ticks, tabanid flies and mosquitoes. The efficacy of the various techniques differs between insects. Biting flies can be particularly difficult to control. Any attached ticks should be removed promptly.

Hunters and others who handle wildlife and their carcasses should use gloves, protect the mucous membranes from contamination (e.g., avoid touching the mouth or eyes, or splashing fluids), and make sure that any breaks in the skin are covered. Hands should be washed with soap and water after handling the animal, and any equipment should be cleaned well. Game meat should be cooked completely, and other foods should be protected from contamination by rodents or other animals. Veterinarians and their staff, as well as sheep ranchers, should use personal protective equipment, such as gloves, and employ good hygiene, when working with animals that may be infected. Care should be taken to avoid bites and scratches. In endemic areas, dust masks might be helpful during activities such as piling hay or mowing the lawn; however, their efficacy against *F. tularensis* has not been evaluated in these situations. To prevent aerosolization, any dead animals should be removed before mowing the lawn. Water should be filtered or treated before drinking. Precautions have also been published for laboratories that work with *F. tularensis*.

A few countries, such as Russia, produce tularemia vaccines for emergency use during outbreaks. These vaccines have some issues and are not employed for routine vaccination. No licensed vaccines are available in most nations.

Morbidity and Mortality

Tularemia is an occupational hazard for hunters, butchers, farmers, fur/ wool handlers, veterinarians, laboratory workers and others who might contact infected animals or their tissues. In some areas such as Martha's Vineyard, Massachusetts, landscape workers seem to be at risk of contracting the pneumonic form. In most countries, tularemia outbreaks are interspersed with periods during which only a few sporadic cases occur. Some outbreaks in humans have been linked to epizootics among wild or domesticated animals (e.g., lemmings, hares, sheep). Clinical cases can occur after direct contact with infected animals, but dead rodents were thought to have contaminated private water supplies during some outbreaks. Extensive human epidemics have occurred during or after wars, when rodent populations may increase and contaminate human food. Unusual sources of organisms have also been reported, such as an outbreak in people exposed to contaminated freshwater crayfish while fishing.

The severity of the illness tends to differ with the subspecies and strain of *F. tularensis*, as well as other factors such as the person's health. *F. tularensis* subsp. *tularensis* is more virulent overall than *F. tularensis* subsp. *holarctica*. However, less pathogenic subtypes of *F. tularensis* subsp. *tularensis* occur in some parts of North America, and infections with these organisms may be comparable to *F. tularensis* subsp. *holarctica*. Ulceroglandular and glandular tularemia, with an estimated case fatality rate of 5% (untreated), are the most common forms of disease caused by both *F. tularensis* subsp. *tularensis* and *F. tularensis* subsp. *holarctica*. These two forms are thought to comprise at least 75-85% of clinical cases. The case fatality rate for respiratory tularemia varies widely, depending on the organism responsible; however, more than 50% of people who develop severe respiratory signs may die without treatment. The typhoidal form has been estimated to occur in 5-15% of cases. It is most often caused by *F. tularensis* subsp. *tularensis* and has the highest case fatality rate. Before antibiotics, the overall case fatality rate for all tularemia cases caused by *F. tularensis* subsp. *tularensis* was estimated to be 5-15%, with some sources suggesting values up to 30%. Far fewer deaths were caused by *F. tularensis* subsp. *holarctica*. Antibiotics have reduced the overall case fatality rate from tularemia to 1-3%.

F. tularensis subsp. *novicida* might be an uncommon human pathogen. Fewer than 20 clinical cases have been described in the literature, as of 2017, and most occurred in people who had concurrent diseases (e.g., diabetes, alcoholism), were immunosuppressed by medications and/or were seriously ill. However, it remains possible that mild illnesses in healthy people have been overlooked or assumed to be caused by other subtypes of *F. tularensis*.

Internet Resources

Centers for Disease Control and Prevention (CDC). Tularemia

European Centre for Disease Prevention and Control (ECDC). Tularaemia

Public Health Agency of Canada. Pathogen Safety Data Sheets

The Merck Manual

The Merck Veterinary Manual

World Organization for Animal Health (WOAH)

WOAH Manual of Diagnostic Tests and Vaccines for Terrestrial Animals

WOAH Terrestrial Animal Health Code

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