REVIEW

Tularemia: an experience of 13 cases including a rare myocarditis in a referral center in Eastern Switzerland (Central Europe) and a review of the literature

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Abstract

Background Tularemia, a zoonotic disease caused by *Francisella tularensis*, can cause a broad spectrum of disease in humans including six major clinical presentations: the ulceroglandular, glandular, oculoglandular, oropharyngeal, typhoidal and pneumonic form. The epidemiology and ecology and thus transmission of tularemia are complex, depending on conditions unique to specific locations.

Case series and methods Thirteen cases with different forms of the disease and one very rare case of a myocarditis are reported, discussed, and reviewed within the scope of current literature.

Conclusion Tularemia is a rare, but emerging disease in Central Europe with glandular and ulceroglandular disease as its predominant forms. Transmission is mainly caused by contact with lagomorphs, rodents and tick bites. However, domestic cats may play an important role in transmission too. Myocarditis is probably a worldwide, but very rare manifestation of tularemia.

Keywords Tularemia · *Francisella tularensis* · Myocarditis · Oculoglandular tularemia · Glandular tularemia · Pulmonary tularemia

Abbreviations

GP	General practitioner
ER	Emergency room
CRP	C-reactive protein
WBC	White blood cells
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
LDH	Lactate dehydrogenase
CK	Creatine kinase
U/ml	Units per milliliter
U/l	Units per liter
G/l	Giga per liter
mg/l	Milligram per liter
ng/l	Nanogram per liter
PCR	Polymerase chain reaction
ECG	Electrocardiogram
CT	Computed tomography
MRI	Magnetic resonance imaging
PET	Positron emissions tomography
I.V.	Intravenous
ELISA	Enzyme-linked immunosorbent assay
Bid	Twice a day
NSAID	Nonsteroidal anti-inflammatory drugs
Ssp.	Subspecies
DNA	Deoxyribonucleic acid
RNA	Ribonucleic acid

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Introduction

Tularemia, a zoonotic disease, also known as rabbit or hare fever, lemming fever or deerfly fever, is caused by *Francisella tularensis*, a Gram-negative, facultative intracellular, coccobacillus [1, 2]. Usually, two subspecies cause human infections: the more virulent *F. tularensis* ssp. *tularensis* (type A), which is mainly limited to North America, and *F. tularensis* ssp. *holarctica* (type B), which appears throughout the northern hemisphere [2].

Transmission occurs by handling infected animals or their feces (by direct contact with the skin or mucosa); ingesting contaminated food or water; inhaling infective particles (aerosols) from contaminated soil, water or plants; or from bites of different arthropods (mainly ticks, mosquitoes and biting flies) [1, 2]. Human-to-human spread has not been documented [2]. Only 10–50 bacteria are needed to cause disease by inhalation or intracutaneous application [3]. Persons at risk are hunters, gamekeepers, foresters, farmers, veterinarians, butchers and laboratory personnel, and also recreational outdoor athletes such as runners or cyclists. The epidemiology and ecology of tularemia are complex and differ depending on the endemic area, as well as the activities, animals and tularemia strains involved [4]. Important sources of human infections are lagomorphs and rodents as well as blood-feeding insects. These vectors may change depending on geographic location. For example, ticks are the most prevalent source of infection in the Rocky Mountain states and eastward in the USA as well as in Central Europe, while biting flies in the USA west of the Rocky Mountains and mosquitoes in Scandinavia are the common modes of transmission [5, 6]. Larger outbreaks are usually observed in countries where the disease is mainly transmitted by mosquitoes (e.g., Sweden, Finland) or by consumption of contaminated water (e.g., Turkey). Smaller outbreaks are reported after consumption of contaminated food, the use of either a lawnmower or a brush cutter, due to epizootic increased rodent populations or the hunting and processing of hare meat [5].

In this case series, 13 cases of tularemia treated in a referral center in Eastern Switzerland are included and 5 of those cases are presented in detail. The epidemiology, transmission and treatment of tularemia in Central Europe are discussed and a very rare case of a myocarditis due to *F. tularensis* is emphasized.

Case presentations

All our cases are summarized in Tables 1, 2 and 3.

Case 1: uleroglandular disease with myocarditis

The day after returning from a 6-day hunting trip in Marienbad, Czech Republic, a 61-year-old otherwise healthy hunter and taxidermist consulted an emergency room doctor because of a painful erythema around a tick bite. He was prescribed peroral amoxicillin/clavulanic acid which his GP switched to doxycycline 2 days later because of nausea and vomiting. Another 2 days later, he was referred with anorexia, self-limiting nightly episode of chest pain with radiation into the left arm, rising CRP and hepatitis. On admission, he was in a good general condition with no fever and no heart murmurs. However, the attending physician discovered a round, reddened, 3×3 cm large and slightly raised patch above the navel with centrally purulent discharge (Fig. 1). Further, slightly tender but not enlarged lymph nodes in the left axilla were present. CRP was 173 mg/l (normal < 8 mg/l), AST 127 U/l (normal < 45 U/l), CK 925 U/l (normal < 170 U/l) and troponin I 3490 ng/l (cut-off < 10 ng/l). In the ECG, non-significant ST-elevations were found. Echocardiography and CT scan of the coronary arteries were normal excluding relevant coronary heart disease. An MRI of the heart showed inflammatory intramural and subepicardial myocardial infiltrations compatible with myocarditis (edema and late-gadolinium enhancement) (Figs. 2, 3). Serologic analysis of *Rickettsia (rickettsii/conorii, typhi), Leptospira interrogans, F. tularensis, Ehrlichia, Coxiella burnetii* and *Borrelia burgdorferi* were negative on admission. Nevertheless, because of high clinical suspicion of tularemia, an antimicrobial treatment with gentamicin I.V. (5 mg/kg/day in 3 doses) and oral doxycycline (100 mg twice daily) was started. Gentamicin was stopped after 2 days (total 6 doses) and the patient was dismissed with instructions to take peroral doxycycline for 3 weeks. In follow-up consultations 2, 4 and 15 weeks later, the patient presented a good state of health and echocardiographies after 3 and 12 weeks showed no functional or structural abnormalities. Laboratory values normalized rapidly under treatment. While follow-up serologic studies for *Borrelia, Coxiella* and *Rickettsiae* remained negative, a seroconversion of *F. tularensis* was documented (IgM > 175.2 U/ml; normal ≤ 10 U/ml and IgG 34.6 U/ml; normal ≤ 10 U/ml) 23 days after onset of symptoms. Seroconversion was confirmed with a western blot assay performed at the German national reference center (Robert-Koch-Institut, Berlin, Germany). Mode of transmission was a tick bite with eschar.

Case 2: pulmonary and pleuritic disease

A 79-year-old male patient entered a local hospital with the following symptoms: progressive dyspnea, worsening cough for 2 days and disorientation. Elevated temperature

Table 1 Overview of form, subspecies, transmission, and risk factors of our cases

Case	Sex and age	Form of tularemia	*Francisella* subspecies	Suspected transmission	Activity and risk factors
1	m, 61	Ulceroglandular with myocarditis	Unknown	Tick bite	Hunter, taxidermist
2	m, 79	Pulmonary	Ssp. *holarctica*	Inhalation of contaminated aerosolized soil	Mowing lawn in rural area near woods
3	f, 13	Oculoglandular	Ssp. *holarctica*	Direct inoculation of contaminated soil	Plucking plants
4	m, 33	Glandular	Ssp. *holarctica*	Domestic cat (scratch)	Keeping of animals (mice, quails, cats) Living near woods
5	m, 25	Pulmonary	Ssp. *holarctica*	Farming and haying	Farmer Keeping of animals (domestic cat, cows, horses, donkey) Immunosuppression with adalimumab (for psoriasis vulgaris)
6	f, 41	Glandular	Unknown	Rodents, domestic cat	Gardening in rural area
7	m, 44	Pulmonary	Unknown	Farming and haying	Farmer with animal husbandry (cows, pigs, cats, dog, rabbits) Living near woods
8	m, 41	Pulmonary	Ssp. *holarctica*	Unknown	Living near woods Spending a lot of time outdoors (including motorbike tour in Northern Italy)
9	m, 78	Ulceroglandular with possible meningoencephalitis	Ssp. *holarctica*	Unknown	Keeping of animals (domestic cat, rabbits) Often in woods
10	m, 35	Glandular	Unknown	Unknown	Farmer Keeping of animals (cows, calves)
11	m, 68	Ulceroglandular	Unknown	Tick bite	Timber felling
12	f, 62	Ulceroglandular	Unknown	Unknown	Keeping of animals (hares, sheep, dogs)
13	m, 70	Glandular or pharyngeal	Ssp. *holarctica*	Tick bite	Recreational activities in woods Party in a forest cabin Contact with mice

(38.1 °C) and a pulmonary crepitation over the right lung were noted. Radiography revealed an infiltration in the right lung and laboratory findings demonstrated an elevated CRP of 330 mg/l, slightly elevated liver enzymes, elevated WBC with 12.9 G/l (normal 4–10 G/l) and low platelets with 102 G/l (normal 150–300 G/l). An empirical antimicrobial treatment with amoxicillin/clavulanic acid I.V. and peroral clarithromycin was initiated on the assumption of community-acquired pneumonia. A pleuritic effusion needed to be punctured three times with no evidence of empyema. On day 7 after admission, blood cultures showed growth of a Gram-negative coccobacillus, and 16s-RNA gene sequencing identified *F. tularensis* ssp. *holarctica*. Serological analysis confirmed pneumonic tularemia by positive enzyme immunoassay (SERION ELISA classic©) for *F. tularensis* (IgM > 11383 U/ml and IgG 80.3 U/ml). A 14-day treatment regimen with oral doxycycline (100 mg twice daily) was prescribed in the already asymptomatic patient. He recovered

without complications. Twelve days before admission, the patient was mowing the lawn in a Swiss rural area near the woods; therefore, inhalation of contaminated aerosolized soil was assumed to be the route of transmission.

Case 3: oculoglandular disease

For 1 day, a 13-year-old girl presented with fever, sore throat, a reddened eye and a swollen eyelid on the right side. Her GP began treatment with peroral amoxicillin/clavulanic acid. An ophthalmologist reported severe papillary conjunctivitis with mucous discharge, swelling of the lower and upper lids and a submandibular lymphadenopathy. A CT scan of the head showed an orbital cellulitis without suppuration. A topical antimicrobial treatment with ofloxacin and polymyxin/neomycin eye drops was additionally started. In a swab of the conjunctiva, culture and PCR were positive for *F. tularensis* ssp. *holarctica*. Antimicrobial treatment was

Table 2 Clinical manifestation, findings, and complications of our cases

Case	Clinical manifestation	Findings	Diagnosis by	Probable or definite case	Interventions and complications
1	Erythema with eschar, chest pain, anorexia	Tender lymph nodes of left axilla; Inflammatory subepicardial myocardial infiltrations (MRI)	Seroconversion; Western blot assay	Definite	Myocarditis
2	Fever, dyspnea, cough	Infiltrations in right lung (X-ray)	Serology; Blood cultures (RNA gene sequencing)	Definite	Puncture of pleuritic effusion
3	Fever, sore throat, reddened eye, swelling of lids	Submandibular lymphadenopathy; Orbital cellulitis without suppuration (CT scan)	Culture and PCR (swab of conjunctiva)	Definite	None
4	Fever, neck swelling	Submandibular and cervical lymphadenopathy; Purulent lymphadenopathy with histologically caseating granulomas	Serology; Eubacterial PCR (lymph node)	Definite	Surgical lymph node excision; Relapse of purulent lymphadenopathy
5	Intermittent fever, chills, night sweats, loss of weight, diarrhea, headaches, dysgeusia, painful lymph node (supraclavicular right)	Painful lymph node supraclavicular right; Enhancing large tumorous mass of right hilus, infiltrations in left and right upper lung lobe, mediastinal lymphadenopathy (CT/PET scan); Central necrotizing, epithelioid cell granulomas (lymph node)	Seroconversion; PCR (lymph node)	Definite	Mediastinoscopy with lymph node excision
6	Fever, sore throat, swelling in right axilla	Right axillary lymphadenopathy; Necrotizing nearly caseous epithelioid cell granulomas (lymph node)	Serology; PCR (lymph node)	Definite	Surgical lymph node excision
7	Fever, night sweats, loss of weight, cough, right-sided chest pain	Hilomediastinal lymphadenopathy, infiltrations in right lower lobe, tumorous mass and nodules in right lower lobe (CT/PET scan); Necrotizing and granulomatous inflammation (lymph node)	Serology	Probable	Bronchoscopic and endosonographic lymph node biopsy
8	Fever, aching limbs, dyspnea	Solid tumorous mass and two pulmonary nodules in upper left lobe, thoracic lymphadenopathy (CT scan); Lymphoid and granulomatous inflammation (lymph node)	PCR (lymph node)	Definite	Sepsis; Acute kidney failure (AKIN 2); Bronchoscopic lymph node biopsy
9	Anorexia, fatigue, frontal headache, night sweats, diarrhea, fever, loss of weight, parkinsonian movement disorder, psychomotor retardation, swelling and ulcer in right axilla	Eschar right axilla; Chronic granulomatous inflammation (lymph node); Parieto-occipital meningitis (MRI); Cerebrospinal fluid (CSF): mononuclear pleocytosis (108/µl), normal CSF/serum ratio for *F. tularensis* antibodies; CSF PCR negative for tularemia	Serology; PCR (lymph node)	Definite	Surgical lymph node excision; Possible meningoencephalitis; Possible infect-triggered atypical Parkinson syndrome

Table 2 (continued)

Case	Clinical manifestation	Findings	Diagnosis by	Probable or definite case	Interventions and complications
10	Slightly painful swelling in left axilla	Left axillary lymphadenopathy Granulomatous inflammation with necrosis (lymph node)	Serology	Probable	None
11	Fever, chills, left-sided flank pain, dysuria, painful scrotal swelling, ulcer on left lower leg	Retroperitoneal, iliac and inguinal lymphadenopathy	Seroconversion	Definite	None
12	Fever, chills, painful and reddened swelling on the right upper arm, painful swelling in right axilla	Suppurative lymphadenopathy right axilla	Serology	Probable	Surgical abscess drainage
13	Fever, sore throat, swelling of the neck, night sweats	Cervical lymphadenopathy Granulomatous inflammation (lymph node)	Serology PCR (lymph node)	Definite	Surgical incision and abscess drainage

switched to peroral ciprofloxacin (500 mg twice daily) for 14 days with complete resolution. Four days before presentation, she was plucking goldenrod with her school class and rubbed her right eye because she noted an insect in her eye. Therefore, the route of transmission was considered to be direct inoculation of contaminated soil in the affected eye.

Case 4: glandular disease

After a 33-year-old man had a fever and sore throat for 5 days, he went to his GP and was prescribed peroral amoxicillin/clavulanic acid. Four days later, he went to the ER with persistent symptoms and axillary swollen lymph nodes. Serology (ELISA; SERION ELISA classic©) for *F. tularensis* was positive (IgM 180.9 U/ml and IgG 154.6 U/ml). The physician started the patient on an antimicrobial treatment with gentamicin I.V. (5 mg/kg body weight once daily) for 5 days and peroral doxycycline (100 mg twice daily). Nineteen days later, an excision of a conglomerate of axillary lymph nodes was performed. Cultures of the nodes were negative, but PCR of two separate biopsies identified *F. tularensis* ssp. *holarctica*. Histological report described lymph nodes with necrotizing nearly caseous epithelioid cell granulomas; Ziehl-Neelsen stain was negative. Doxycycline was stopped after a total of 38 days. He recovered completely without further complications. The patient lives at the edge of the woods and sighted foxes, deer and hares regularly. Further, he kept several healthy pets, specifically mice, quails and cats. About 7 days before his fever started, the patient's cat scratched him on the forearm of the affected axilla. His cat was often outdoors and chased mice regularly. Further, he remembered that he pinched his forefinger of the same side while handling the cage of his fancy mice (*mus musculus domesticus*); however, they never left the cage. Therefore, transmission was assumed to come from the scratch of his domestic cat.

Case 5: atypical pulmonary disease

A 25-year-old man, who was already suffering from psoriasis treated with adalimumab, went to an ER in a local hospital after experiencing intermittent fever and chills for 4 days, anorexia and weight loss, night sweats, diarrhea, dysuria, headaches and a painful lymph node at the right neck. Laboratory findings showed an elevated CRP of 160 mg/l and normal procalcitonin 0.1 µg/l (normal < 0.5 µg/l), slightly elevated liver enzymes and LDH (558 U/l; normal < 265 U/l), elevated WBC with 15.2 G/l and elevated platelet count. Blood and stool cultures showed no bacterial growth. A CT scan of the chest showed a mass near the right hilus, infiltrations in the left and right upper lung lobe, a mediastinal lymphadenopathy and a splenomegaly. A lymphoma or pulmonary neoplasia was suspected

Table 3 Antibiotic treatment and follow-up of our cases

Case	Antimicrobial treatment	Total treatment duration (days)	Follow-up	Treatment of already asymptomatic patient
1	GEN I.V. (5 mg/kg of body weight/day in three doses for 2 days) DOX p.o. (100 mg b.i.d. for 21 days)	23	Restitutio ad integrum	No
2	DOX p.o. (100 mg b.i.d. for 14 days)	14	Restitutio ad integrum	Yes
3	Ofloxacin and polymyxin/neomycin eye drops CIP p.o. (500 mg b.i.d. for 14 days)	14	Restitutio ad integrum	No
4	GEN I.V. (5 mg/kg of body weight q.d. for 5 days) DOX p.o. (100 mg b.i.d. for 38 days)	43	Restitutio ad integrum	No
5	CIP p.o. (750 mg b.i.d. for 18 days)	18	Restitutio ad integrum	No
6	DOX p.o. (100 mg b.i.d. for 21 days and 14 days) CIP p.o. (750 mg b.i.d. for 14 days)	49	Persistent enlarged cervical lymph nodes	No
7	CIP p.o. (750 mg b.i.d. for 14 days)	14	Restitutio ad integrum	Yes
8	DOX p.o. (100 mg b.i.d. for 21 days)	21	Restitutio ad integrum	No
9	CIP p.o. (750 mg b.i.d. for 28 days)	28	Restitutio ad integrum	No
10	DOX p.o. (100 mg b.i.d. for 24 days) CIP p.o. (500 mg b.i.d. 6 days)	30	Restitutio ad integrum	No
11	DOX p.o. (100 mg b.i.d. for 14 days)	14	Restitutio ad integrum	No
12	DOX p.o. (100 mg b.i.d. for 14 days)	14	Restitutio ad integrum	No
13	DOX p.o. (100 mg b.i.d. for 14 days) CIP p.o. (750 mg b.i.d. for 21 days)	35	Restitutio ad integrum	No

GEN gentamicin, *DOX* doxycycline, *CIP* ciprofloxacin, *Q.d.* once a day, *B.i.d.* twice a day, *I.V.* intravenous, *P.o.* per os

Fig. 1 Eschar above the navel of the patient in Case 1

Fig. 2 Four chamber view, T2w Tirm dark blood shows edema intramural in the ventricular septum and patchy subepicardial in the lateral wall of the left ventricle

and the patient was referred for oncologic evaluation. An 18F-fluorodeoxyglucose (FDG)-PET/CT scan showed an FDG-enriching, 4.8 ×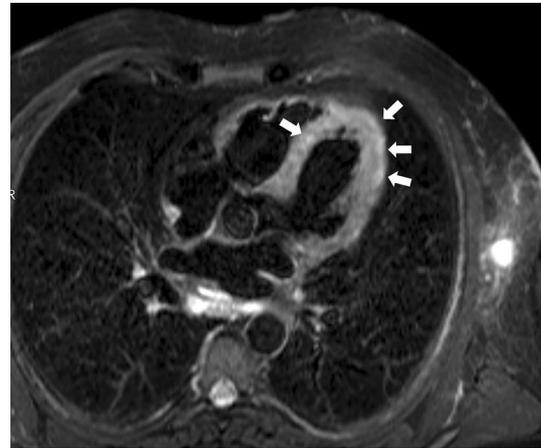 3.3 cm large tumorous mass and mediastinal and retroperitoneal lymphadenopathy. After inconclusive results of transbronchial biopsies, a mediastinoscopy was performed, wherein lymph nodes with central necrotizing epithelioid cell granulomas without evidence of a neoplasia were found. Eubacterial PCR of the biopsy was positive for *F. tularensis* ssp. *holarctica*. A seroconversion of *F. tularensis* could be documented (IgM < 4 to 124.8 U/ml and IgG < 3 to 160.3 U/ml. (ELISA; SERION ELISA classic©)). Peroral antibiotic treatment with ciprofloxacin
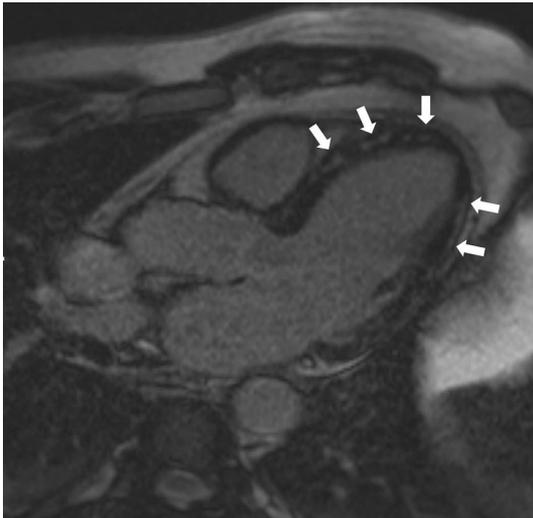
Fig. 3 Three-chamber view, T1w late-gadolinium enhancement (LGE) shows patchy LGE intramural of the ventricular septum and subepicardial of the lateral wall of the left ventricle

(750 mg twice a day) was prescribed for 18 days. A CT scan after 6 weeks showed a nearly total regression of the pulmonary mass and lymphadenopathy. We assume a pulmonary tularemia with atypical presentation (as pulmonary mass with initial concern of a neoplasia). Mode of transmission remains unclear; however, because the patient was a farmer in a rural area and neither tick bite nor contact with rodents or cat scratch was observed, aerosol inhalation of infective particles can be presumed as the route of transmission. The risk factor was immunosuppressive therapy.

Cases 6–13

Cases 6–13 are summarized in Tables 1, 2 and 3.

Methods

Case definition

A case of tularemia was defined as a possible, a probable or a definite case. Besides the appropriate clinical signs and symptoms of the different forms of tularemia and an exposure to a common source for a possible case (e.g., animal, tick bite, contaminated food or drinking water), a laboratory confirmation was necessary: for a probable case, a single elevated serological titer was required; and for a definite case, a positive PCR or isolation of *F. tularensis* in a biological sample or a seroconversion or fourfold increase of serum antibody titer was required in two samples with a minimum interval of 2 weeks [7].

Discussion of our cases within the scope of the literature

Morbidity and mortality

F. tularensis, named after Tulare county in California where it was originally described by G.W. McCoy in 1911 and after E. Francis, who isolated the bacteria in the blood of ill patients in 1919, can be divided into four subspecies: ssp. *tularensis, holarctica, mediasiatica* and *novicida* [2, 3]. Of these four, ssp. *tularensis* (type A strains) and ssp. *holarctica* (type B strains) are related to most cases of tularemia. Traditionally, type A strains, which are found mainly in Northern America (USA and Canada), are reported to be highly virulent and have been classified as potential agents for bioterrorism because of a fatality rate up to 30% in cases of untreated respiratory disease. Type B strains tend to be much less virulent and are found throughout the whole Northern Hemisphere, but seem to be emerging in the Southern Hemisphere as in Tasmania [8, 9]. Tularemia can be a debilitating disease with prolonged sickness, but death is a very rare event in Europe after patients receive appropriate antibiotic treatment [9]. Recent studies suggest that mortality varies according to genotype (especially infection with genotype A1b results in highest mortality in the USA) and that distributions of genetic subtypes were associated with specific tularemia vectors and hosts [10, 11].

Our experience shows that morbidity in infection with the subspecies *holarctica* is predominantly due to the ulceroglandular and glandular forms where, despite an appropriate antimicrobial treatment, a surgical procedure is often needed either to make a diagnosis by biopsy and histological examination or to drain an abscess formation or remove a persistent or relapsing lymphadenopathy. The antibiotic treatment often had to be extended and persistent glandular swelling can occur. In pulmonary tularemia, an improvement of symptoms occurred even without proper antibiotic treatment. Outcome after treatment even in patients with atypical pulmonary tularemia, such as pulmonary masses or nodules, was good; no morbidity after treatment was observed even in an immunocompromised patient treated with adalimumab. Similar cases of atypical pulmonary presentation with initial concern of a malign neoplasia are described in a few cases, most of them with a good outcome after receiving appropriate antimicrobial treatment [12–16]. We saw one case of an ulceroglandular form with possible associated meningoencephalitis and a parkinsonian movement disorder, triggered by this infection, which was regressive after treatment with levodopa. In summary, we experienced neither severe morbidity nor fatal cases, so we assume that morbidity and mortality

seem to be low in Central Europe even in pulmonary and systemic tularemia. Cardiac involvement is discussed in detail below.

Long term reservoirs and mode of transmission

Long-term reservoirs are still not well defined, as the involved animals often develop fatal infections [9]. An aquatic reservoir of the bacteria could exist, as many outbreaks could be attributed to waterborne transmission [9]. Recently, it was speculated that *F. tularensis* does not have a defined reservoir, but rather different biological niches allowing the persistence of the bacterium in the environment. The main niches or amplification hosts would include rodents and lagomorphs, amebae, mosquitoes and ticks [17]. Domestic animals, especially sheep and cats in the USA, might be infected or act as carriers of *F. tularensis* [9]. The numerous host species that are susceptible to infection together with different routes of transmission and the ability to survive in water, humid soil and in carcasses add up to the very efficient transmission of *F. tularensis* and define the diverse epidemiology for different regions [17]. Disease can occur in sporadic cases, but also larger outbreaks in endemic areas are described. Investigations of an outbreak of respiratory tularemia in Sweden in the year 2010 showed both genetically indistinguishable and many different isolates of *F. tularensis*, suggesting specific, but not yet known, environmental factors favorable to an increased transmission of *F. tularensis* rather than an improved feature of one specific clone leading to an outbreak of tularemia [18]. The large geographic distribution of genetically closely related isolates could be associated with bird migration or transportation of aerosolized bacteria by wind in the troposphere over large distances [18].

In published series, the mode of transmission of *F. tularensis* ssp. *holarctica* in Europe could be explained by their two suspected life cycles: (1) a terrestrial life cycle with lagomorphs, rodents and ticks as main vectors in mainly sporadic cases; and (2) an aquatic life cycle, within an aquatic environment which can be contaminated by carcasses or excrement of infected animals, and mosquito-borne, as the main source of infection that often occurs as an outbreak. In Central Europe, including Switzerland, Austria, Germany, France, Hungary, Slovakia and Czech Republic, the most frequent mode of transmission can be derived from the terrestrial life cycle and is mainly by contact with lagomorphs, rodents and ticks [9]. Further, transmission by bites and scratches of domestic cats, which are regularly exposed to arthropods and rodents by their predatory behavior, has been described before in various cases. Owning a cat was a relevant risk factor for acquiring tularemia by direct transmission (bite or scratch) or by an increased exposure to carcasses brought home by a cat [19]. Cats infected with

F. tularensis might be asymptomatic, listless or have fever or anorexia [20]. In a recent survey of privately owned domestic cats in the eastern part of the USA, seroprevalence for *F. tularensis* was 12–24% [21–23]. In a sample of 50 wild-type *F. tularensis* isolates of infected humans or animals in Nebraska (USA), 48% (24/50 isolates) were feline associated, meaning infected humans were linked to cats or cats were infected themselves [22]. Cats were an important source of type A and especially A1b genotypes, which are associated with the highest mortality [10].

In Europe, a high incidence of tularemia is observed in Scandinavian countries (highest in Finland, 7.6 per 100,000), mostly associated with arthropod bites (mainly mosquitoes) or aerosol exposures [7]. Incidences in Central and Southern Europe are lower, varying from 0.07 to 0.19 cases per 100,000 inhabitants and transmission is mainly related to contact with lagomorphs, rodents and ticks [7]. In Switzerland, where since 2004 cases of tularemia must be reported to the Federal Office of Public Health, the incidence is rapidly rising from 0.67 to 1.54 cases per 100,000 inhabitants (total cases: from 57 of 127 cases) from the year 2016 to 2017 [24]. The increasing number of cases could be due to a better awareness of the disease, a better diagnostic approach (e.g., broad spectrum PCR), an increasing population density in rural areas and thus more recreational activities in woody areas with consequently more tick bites or contact with animals and an increased survival of ticks because of warmer winters due to climate change and, thus, a rising level of transmission in higher altitude areas, where a transmission even at 1,700 m above sea level was described [25].

Assumed transmission in our cases varied: three by tick bite, one by inhalation of infective particles, one by direct inoculation of the eye with contaminated soil and at least four probable direct contacts with rodents and/or domestic cats. In some cases, the mode of transmission remained uncertain, but it was notable that many of the patients were farmers. We also found a remarkable accumulation of cases in a geographic area located in eastern Switzerland (districts of Sarganserland and Werdenberg), which leads to the assumption that there must be a special niche for *F. tularensis*. The broad spectrum of transmission allows us assume that besides handling of lagomorphs and rodents and tick-associated disease as the predominant forms, all other modes of transmission must be considered important as well in Central Europe. Especially domestic cats must be considered as relevant players in the transmission of tularemia to humans.

Clinical presentation and diagnosis

After a short incubation time (3–5 days, range 1–21 days), flu-like symptoms can occur [2, 9]. Six major clinical forms are known (Table 4) [1, 2, 9]. Complications and other

manifestations include abscesses (local or brain abscesses), suppurative lymphadenopathy with fistulation, skin rashes (e.g., erythema nodosum or multiforme), otitis media, meningitis, endocarditis, pericarditis and hematogenous spread of the bacteria [9]. The diagnosis is based on clinical suspicion, the local epidemiology, positive serologic tests (micro-agglutination, indirect immunofluorescence assay, ELISA or western blot), a direct isolation and cultural growth or a PCR of *F. tularensis*, e.g., in blood culture, lymph node, skin biopsy or even swabs of wounds, the latter with a sensitivity up to 78% and a specificity of 97% (PCR targeting *tul4* gene) [1, 26]. Serologic diagnosis is challenging, because antibodies are usually not detectable before the second week of disease. Cross-reactivities of antibodies with *Brucella, Proteus* and *Yersinia* species have been described, but are usually not troublesome for tularemia diagnosis because titers to *F. tularensis* are almost always higher [5, 27].

Most of our cases (8 out of 13) presented primarily as glandular or ulceroglandular form, which was to be expected by local epidemiology. Four cases were primary pulmonary. Initially, pulmonary tularemia is often not suspected and is treated as community-acquired pneumonia. Three pulmonary cases presented atypically as a pulmonary mass or nodule and malignancy was suspected. Diagnosis is usually not made before the patient endures multiple medical imaging with relevant radiation exposure (CT scan, PET/CT scan) and invasive procedures. This means not only unnecessary costs and potential complications for the patient, but emotional stress because of a possible diagnosis of cancer. We therefore emphasize that medical providers should consider and look for tularemia early in the course of a compatible clinical presentation. But, it should be noted that CT scans as well as PET/CT scans of pulmonary tularemia can be indistinguishable from malignancy, so that an accurate workup in cases with suspected pulmonary malignancy is important [16]. Only one oculoglandular and one possible pharyngeal case were observed. We also saw two rare manifestations of tularemia: one myocarditis, which is discussed below and one possible meningoencephalitis, but in the latter case, no evidence of *Francisella* could be verified in the cerebrospinal fluid analysis, so that the involvement of the central nervous system in the otherwise definite diagnosis of tularemia remains uncertain.

Our diagnoses were made mainly by serological tests and PCR of lymph node biopsies. A direct growth of bacteria could be documented twice: once in a blood culture of a pneumonic and once in an eye swab from an oculoglandular tularemia. In our series, a surprisingly high number of biopsies (three out of eight) showed caseous or epithelioid cell granulomas, which could be easily confused with tuberculosis. In the others, suppurative inflammation without granuloma could be seen. The literature describes reactive changes without necrosis in the early stage of infection, with abscess

Table 4 Clinical forms, signs, symptoms and transmission of tularemia

Clinical form	Signs and symptoms	Transmission	Case frequency in literature (in %) [7]
Glandular	Regional lymphadenopathy (often with fistula and abscesses); malaise; fever	Tick bites, insect bites, contact with infected animals or infected animal material	46
Ulceroglandular	Ulceration or eschar of the skin; regional suppurative lymphadenopathy (often with fistula and abscesses); malaise; fever	Tick bites, insect bites, contact with infected animals or infected animal material	26
Oculoglandular	Conjunctival ulceration or conjunctivitis (mostly unilateral); preauricular, submandibular or cervical lymphadenopathy; malaise; fever	Smear or airborne infection after contact with infected animals or infected animal material, contaminated water or aerosol containing pathogen	2
Oropharyngeal (and gastrointestinal)	Pharyngitis; stomatitis; tonsillitis; submandibular lymphadenitis (mostly unilateral); abdominal pain; diarrhea (intestinal hemorrhage possible); nausea; malaise; fever	Ingestion of contaminated food/water, inhalation of aerosol containing pathogen	6
Pulmonal or pneumonic	Pneumonia or pulmonal masses or nodules; dyspnoea; cough; chest pain; pleuritis; hilar lymphadenopathy; malaise; fever	Inhalation of aerosol containing pathogen or secondary by hematogenic spread	10
Generalized, systemic or typhoidal	High fever and septic clinical presentation without local findings; possible gastrointestinal symptoms (e.g., abdominal pain, mesenteric lymphadenopathy)	All ways of transmission possible	10

formation 2 weeks later and small epithelioid cell granuloma with necrosis in the center after 2–6 weeks. Caseous granuloma was detected after the fourth week of disease [28]. In a Turkish case series, only 8% (12/157 cytology findings) showed caseous necrosis [28].

Antimicrobial treatment

There are guidelines for antimicrobial treatment of different forms of tularemia from 2007, which were mainly adopted from a consensus meeting in the USA a few years earlier [29, 30]. According to these, the first choices for treatment are bactericidal antibiotics such as streptomycin or gentamicin for 10 days. Doxycycline or ciprofloxacin are listed as alternative choices, particularly for non-severe cases. However, in Europe, where infections are mostly caused by *F. tularensis* ssp. *holarctica* and patients are often treated as outpatients, ciprofloxacin is often considered as first-line treatment [9]. Ciprofloxacin seems to be ideal as it is bactericidal, has a very low minimal inhibitory concentration in vitro and has a high intracellular concentration in macrophages [31, 32]. Further, quinolones have good bioavailability when given perorally and are generally well tolerated. In addition, relapse rates are considered low; in fact, recent studies indicate that relapse rates for quinolones are similar to or even lower than those with aminoglycosides [33–35]. Suggested peroral doses of ciprofloxacin in case series range from 1000 to 1500 mg daily. However, one study demonstrated that a 750 mg bid was superior to a 500 mg bid dose [33]. As this finding derives from a retrospective case series, one has to interpret the finding with caution. In clinical practice, we usually prefer 1500 mg daily when tolerated by patients. Doxycycline, which is an alternative agent for peroral therapy, is considered to be less effective because relapses are more prevalent [34, 36–38]. In clinical situations, when someone presents with erythema or fever after a tick bite and where several tick-borne diseases are a concern, doxycycline still can be a good empirical choice in our opinion. In contrast to ciprofloxacin or doxycycline, aminoglycosides have to be given intravenously or intramuscularly and have more adverse side effects. In addition, theoretical disadvantages of aminoglycosides for its use in tularemia with suppuration include poor activity in acidic and hypoxic environments and poor intracellular penetration [39]. As a β-lactamase producer, *F. tularensis* are resistant to β-lactam antibiotics [9]. Furthermore, macrolides should not be given, as strains in Switzerland as well as in other parts of Europe are often resistant and clinical data are scarce and not promising [29, 31, 32, 40, 41]. However, some authors consider macrolides as valid treatment in pregnancy when susceptibility can be assumed [42, 43]. Recommended treatment duration is 10 days for aminoglycosides and 14 days for doxycycline and quinolones [29]. In clinical practice,

however, while doxycycline is mostly given for at least 14 days, quinolones are often prescribed for a 10-day course with good outcome [44, 45]. We are not aware of studies that compare different treatment durations.

An unanswered question is whether asymptomatic patients with a retrospective or accidental diagnosis should be treated with a full course of antibiotics that are active against *F. tularensis*. In most case reports, even asymptomatic patients are treated with a full course of antibiotics because of the fear of a relapse [46], as we did in two pulmonary cases. However, there are reports of good outcomes without treatment in asymptomatic patients [41, 47]. In our daily practice, we have never seen a relapse of tularemia in patients with assumed, previously healed tularemia without antibiotic treatment or in patients with tularemia after established immunosuppression, which could be a clue for latent infection as in other intracellular infections. According to serologic studies, though, most cases of tularemia remain undiagnosed and thus not treated with effective antibiotics; therefore, the chance to see these patients in clinical practice in case of relapse or reactivation of the infection would be high [48].

Antibiotic prophylaxis, e.g., with ciprofloxacin can be discussed after proven exposure to *F. tularensis*. Currently, there is no efficient vaccine available [9].

Our antibiotic regimen and the duration of treatment varied. We used doxycycline or ciprofloxacin perorally for both 14 and 21 days in uncomplicated cases of ulceroglandular, glandular, pulmonary and oculoglandular disease and experienced favorable outcomes. In five (ulcero-)glandular cases, we extended the antibiotic treatment individually for up to 50 days because the patients displayed a relapse or persistent lymph node swelling or suppuration. Several times after the diagnosis of tularemia, we switched the initially chosen treatment of doxycycline, empirically chosen because of activity against other suspected tick-associated diseases, to ciprofloxacin because of the patient's poor response to the initial therapy. It remains unclear, however, if the patient's improvement was due to the switch in medication or rather to a surgical intervention, which was often necessary. Also, we rarely used aminoglycosides based on local epidemiology with the less virulent ssp. *holarctica*, because many of our cases were uncomplicated and thus treated as outpatients.

Surgical evaluation and treatment

In Europe, where the ulceroglandular and glandular forms of tularemia predominate, management of enlarged lymph nodes is important because up to a third of patients with lymphadenopathy eventually develop chronic lymph node suppuration or skin fistula [9]. Lymph node complications were also the reason for repeated or prolonged courses of antimicrobial treatment in our case series as in other cases

[43]. Hence, timely surgical evaluation is of importance for faster cure and rational antimicrobial use. One factor for lymph node complications is delayed presentation and delayed antibiotic treatment [28, 34, 38]. Ultrasonography is a rational tool for evaluation of lymph nodes. Marked enlargement of the dominant lymph node, intranodal necrosis or suppuration should prompt surgical evaluation [33, 38]. When antimicrobial treatment is started, a patient's clinical response should be regularly evaluated and new suppuration, growth or stagnation of lymph nodes' size or fistulation should initiate surgical reevaluation [28].

In five out of nine glandular or ulceroglandular diseases in our series, a surgical intervention had to be performed. This reflects the importance of an early diagnostic and therapeutic surgical evaluation for best success of therapy.

Myocarditis

Literature review

For identifying published case reports of tularemia and myocarditis, PubMed and Scopus databases were searched using the search string *(Francisella OR tularemia) AND (pericarditis OR myocarditis OR perimyocarditis)*. No restriction of the time period of publication was applied.

Concerning myocarditis, only two cases have been published thus far, one case in the Spanish-language medical literature and one case in the German-language medical literature. In the Spanish case, a 74-year-old male with fever and chest pain, elevated CRP and troponin I, and initially normal echocardiography and negative ergometry associated with tularemia (confirmed by seroconversion from an initially negative titer to 1/1024 after 2 weeks), who was treated with ciprofloxacin (1500 mg/day for 10 days), developed a dilated cardiomyopathy with severely reduced left ventricular ejection fraction (30%) and left bundle branch block with need of a cardiac resynchronization therapy after a few months [49]. The chronologic coincidence with the tularemia, the lack of known heart disease and no evidence of another cause of myocarditis (including negative serologies for several other viral and bacterial agents) made the assumed diagnosis of a myocarditis due to *F. tularensis* the most probable. Transmission of disease in this case was unknown.

In the second published case, a 52-year-old Swiss male presented with fever, chest and limb pain, headache and submandibular enlarged lymph nodes. He was initially treated with NSAID due to a suspected viral perimyocarditis (diagnosed by positive troponin T, typical ECG changes, echocardiography and MRI) with complete resolution of the cardiac symptoms. However, because of persistent fever, night sweats, fatigue and growing lymphadenopathy, the diagnosis of a glandular tularemia by seroconversion was made.

The outcome was favorable after an antibiotic treatment (tobramycin I.V. 5 mg/kg once daily for 5 days, followed by peroral doxycycline 100 mg twice daily for 4 weeks) and surgical drainage [50]. There was a timely association between the perimyocarditis and the glandular tularemia, but no other possible etiologies of the myocarditis were discussed and resolution of cardiac symptoms occurred just by treatment with NSAID and not by antibiotic treatment.

One case of a post-mortem diagnosis of a myocarditis due to *F. tularensis* was published decades ago without further details of clinical course and diagnosis [51]. Other historically published papers discussed *F. tularensis* as a possible pathogen for a so-called *granulomatous or isolated myocarditis* in autopsy findings, where no organism could be found microscopically or on culture, for example, tuberculous bacilli or spirochetes, and which resembled tularemic granulomatous myocarditis in experimental settings in hares [52–55].

Metabolic alterations in the myocardium during infection with *F. tularensis* even without myocarditis could be demonstrated in mice suspected as part of the systemic catabolic response [56]. *F. tularensis*-DNA could be detected by PCR in fixed tissue of both human and animal heart muscle [27]. The above data suggest that an inflammatory involvement of the heart in tularemia is common, but the clinical significant development of a (peri-)myocarditis seems to be a rare event.

Our Case 1 is the third case overall and the first case published in the English-language medical literature with myocarditis due to *F. tularensis* documented with MR-imaging. The diagnosis of myocarditis was confirmed by elevated troponin I and typical changes in ECG and MRI. The aspect of the skin lesion following the tick bite and the axillary lymphadenopathy was suggestive of a tick-associated disease. The main pathogenic agents transferred by ticks in Europe include borreliosis, tularemia, ehrlichiosis, anaplasmosis and tick-borne encephalitis. Furthermore, the region of a tick bite can become superinfected by skin bacteria, such as staphylococci or streptococci. In our case, a seroconversion for *F. tularensis* could be documented and a confirmatory assay by western blot was found to be positive. This seroconversion, together with the negative serologic analysis of the above discussed tick-associated infectious agents, makes a myocarditis by *F. tularensis* very likely. The clinical outcome was good after treatment with gentamicin for 2 days and doxycycline for 21 days.

Conclusions

Thirteen cases of different clinical presentations of tularemia in Eastern Switzerland were presented. Infection with *F. tularensis* seems to be still underdiagnosed because of the various and unspecific clinical symptoms, the rarity of the

disease and the delayed diagnosis because of the difficulty of a cultural growth of the bacteria; however, the incidence in Switzerland is rapidly rising. Ulceroglandular and glandular disease is the predominant form of disease in Central Europe often associated with relapsing and purulent lymphadenopathy. Early surgical evaluation is important to prevent local complications, relapses and prolonged antibiotic treatment. Atypical pulmonary tularemia has to be considered as a differential diagnosis for assumed pulmonary neoplasia.

Clinically relevant myocardial involvement is probably a very rare event and often not recognized. Tularemia with cardiac involvement should be considered in patients in endemic areas of *F. tularensis* with signs and symptoms of a myocarditis and in patients suffering from other clinical forms of tularemia with cardiac symptoms.

Besides tick bites and direct contact with lagomorphs or rodents, domestic cats should be considered an important vector of transmission of *F. tularensis*. Therefore, cat owners should be aware and protect themselves from bites or scratches and wear protective gloves when handling possibly infected prey.

Further studies with more cases are needed to draw conclusions of the optimal treatment regime and duration of tularemia, especially tularemic myocarditis.

Compliance with ethical standards

Conflict of interest We received no financial support for this work. We state that there is no conflict of interest.

Informed consent Written informed consent for publication of the cases and images was obtained from all the patients.

References

1. Ellis J, Oyston PCF, Green M, Titball RW. Tularemia. Clin Microbiol Rev. 2002;15:631–46.
2. Tärnvik A, Berglund L. Tularaemia. Eur Respir J. 2003;21:361–73. https://doi.org/10.1183/09031936.03.00088903.
3. Tularämie, Hasenpest—Ein Überblick. Bundesamt für Gesundh. BAG. 2012. https://www.bag.admin.ch/bag/de/home/themen/mensch-gesundheit/uebertragbare-krankheiten/infektionskrankheiten-a-z/tularaemie.html. Accessed 5 Jan 2017.
4. Keim P, Johansson A, Wagner DM. Molecular epidemiology, evolution, and ecology of *Francisella*. Ann N Y Acad Sci. 2007;1105:30–66. https://doi.org/10.1196/annals.1409.011.
5. Penn RL. 229—Francisella tularensis (Tularemia). In: Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 2015. [cited 2017 Aug 20]. pp. 2590–2602.e3. http://www.sciencedirect.com/science/article/pii/B9781455748013002290.
6. Sjöstedt A. Tularemia: history, epidemiology, pathogen physiology, and clinical manifestations. Ann N Y Acad Sci. 2007;1105:1–29. https://doi.org/10.1196/annals.1409.009.
7. Mailles A, Vaillant V. 10 years of surveillance of human tularaemia in France. Eurosurveillance 2014;19:20956. https://doi.org/10.2807/1560-7917.ES2014.19.45.20956
8. Jackson J, McGregor A, Cooley L, Ng J, Brown M, Ong CW, et al. Francisella tularensis subspecies holarctica, Tasmania, Australia, 2011. Emerg Infect Dis. 2012;18:1484–6.
9. Maurin M, Gyuranecz M. Tularaemia: clinical aspects in Europe. Lancet Infect Dis. 2016;16:113–24.
10. Kugeler KJ, Janusz AM, Staples JE, Kubota KA, Chalcraft LG, Petersen JM. Molecular epidemiology of *Francisella tularensis* in the United States. Clin Infect Dis. 2009;48:863–70. https://doi.org/10.1086/597261.
11. Farlow J, Wagner DM, Dukerich M, Stanley M, Chu M, Kubota K, et al. Francisella tularensis in the United States. Emerg Infect Dis. 2005;11:1835–41.
12. Alias T, Fallahzadeh MK, Berhe M. Tularemia presenting as pulmonary nodules in an immunocompromised patient. Bayl Univ Med Cent Proc. 2017;30:175–6.
13. Franzen D, Müller F, Bode PK. Lung mass and tularaemia. QJM. 2016;109:417–8.
14. Odegaard K, Boersma B, Keegan J. Atypical presentations of tularemia. S D Med U S. 2017;70:207–9.
15. Naughton M, Brown R, Adkins D, DiPersio J. Tularemia—an unusual cause of a solitary pulmonary nodule in the post-transplant setting. Bone Marrow Transpl. 1999;24:197–9.
16. Fachinger P, Tini GM, Grobholz R, Gambazzi F, Fankhauser H, Irani S. Pulmonary tularaemia: all that looks like cancer is not necessarily cancer—case report of four consecutive cases. BMC Pulm Med. 2015;15:1–6.
17. Genchi M, Prati P, Vicari N, Manfredini A, Sacchi L, Clementi E, et al. *Francisella tularensis*: no evidence for transovarial transmission in the tularemia tick vectors dermacentor reticulatus and ixodes ricinus. PLoS One. 2015;10:e0133593.
18. Johansson A, Lärkeryd A, Widerström M, Mörtberg S, Myrtännäs K, Öhrman C, et al. An outbreak of respiratory tularemia caused by diverse clones of *Francisella tularensis*. Clin Infect Dis. 2014;59:1546–53.
19. Eliasson H, Lindbäck J, Pekka Nuorti J, Arneborn M, Giesecke J, Tegnell A. The 2000 tularemia outbreak: a case-control study of risk factors in disease-endemic and emergent areas, Sweden. Emerg Infect Dis. 2002;8:956–60.
20. Capellan J, Fong IW. Tularemia from a cat bite: case report and review of feline-associated tularemia. Clin Infect Dis. 1928;16:472–5.
21. Petersson E, Athlin S. Cat-bite-induced *Francisella tularensis* infection with a false-positive serological reaction for *Bartonella quintana*. JMM Case Rep. 2017;4:4–7. https://doi.org/10.1099/jmmcr.0.005071.
22. Larson MA, Fey PD, Hinrichs SH, Iwen PC. *Francisella tularensis* bacteria associated with feline tularemia in the United States. Emerg Infect Dis. 2014;20:2068–71.
23. Shaw SE, Birtles RJ, Day MJ. Arthropod-transmitted infectious diseases of cats. J Feline Med Surg. 2001;3:193–209.
24. Federal Office of Public Health FOPH Switzerland. https://www.bag.admin.ch/bag/de/home/zahlen-undstatistiken/zahlen-zu-infektionskrankheiten.exturl.html. Accessed 1 Dec 2017.
25. Ernst M, Pilo P, Fleisch F, Glisenti P. Tularemia in the Southeastern Swiss Alps at 1,700 m above sea level. Infection. 2015;43:111–5.
26. Tärnvik A, Chu MC. New approaches to diagnosis and therapy of tularemia. Ann N Y Acad Sci. 2007;404:378–404.
27. Lamps LW, Havens JM, Sjostedt A, Page DL, Scott MA Histologic and molecular diagnosis of tularemia: a potential bioterrorism agent endemic to North America. Mod Pathol. 2004;17:489–95.
28. Erdem H, Ozturk-Engin D, Yesilyurt M, Karabay O, Elaldi N, Celebi G, et al. Evaluation of tularaemia courses: a multicentre

study from Turkey. Clin Microbiol Infect. 2014;20:O1042–51. https://doi.org/10.1111/1469-0691.12741.

29. Dennis DT, Inglesby TV, Henderson DA, Bartlett JG, Ascher MS, Eitzen E, et al. Tularemia as a biological weapon: medical and public health management. JAMA U S. 2001;285:2763–73.

30. WHO guidelines on tularaemia. WHO Libr. Cat. Data. 2007.

31. Caspar Y, Hennebique A, Maurin M. Antibiotic susceptibility of *Francisella tularensis* subsp. *holarctica* strains isolated from tularaemia patients in France between 2006 and 2016. J Antimicrob Chemother Engl. 2017;73:687–91.

32. Tomaso H, Hotzel H, Otto P, Myrtennas K, Forsman M. Antibiotic susceptibility in vitro of *Francisella tularensis* subsp. *holarctica* isolates from Germany. J Antimicrob Chemother England. 2017;72:2539–43.

33. Ulu-Kilic A, Gulen G, Sezen F, Kilic S, Sencan I. Tularemia in central Anatolia. Infect Ger. 2013;41:391–9.

34. Meric M, Willke A, Finke E-J, Grunow R, Sayan M, Erdogan S, et al. Evaluation of clinical, laboratory, and therapeutic features of 145 tularemia cases: the role of quinolones in oropharyngeal tularemia. APMIS Den. 2008;116:66–73.

35. Pérez-Castrillón JL, Bachiller-Luque P, Martín-Luquero M, Mena-Martín FJ, Herreros V. Tularemia epidemic in northwestern Spain: clinical description and therapeutic response. Clin Infect Dis U S. 2001;33:573–6.

36. Enderlin G, Morales L, Jacobs RF, Cross JT. Streptomycin and alternative agents for the treatment of tularemia: review of the literature. Clin Infect Dis. 1994;19:42–7.

37. Penn RL, Kinasewitz GT. Factors associated with a poor outcome in tularemia. Arch Intern Med U S. 1987;147:265–8.

38. Eliasson H, Back E. Tularaemia in an emergent area in Sweden: an analysis of 234 cases in five years. Scand J Infect Dis Engl. 2007;39:880–9.

39. Risi GF, Pombo DJ. Relapse of tularemia after aminoglycoside therapy: case report and discussion of therapeutic options. Clin Infect Dis U S. 1995;20:174–5.

40. Origgi FC, Frey J, Pilo P. Characterisation of a new group of *Francisella tularensis* subsp. *holarctica* in Switzerland with altered antimicrobial susceptibilities, 1996 to 2013. Eurosurveillance 2014;19:1–10.

41. Borde JP, Zange S, Antwerpen MH, Georgi E, von Buttlar H, Kern WV, et al. Five cases of vector-borne *Francisella tularensis holarctica* infections in south-western Germany and genetic diversity. Ticks Tick Borne Dis Neth. 2017;8:808–12.

42. Dentan C, Pavese P, Pelloux I, Boisset S, Brion J-P, Stahl J-P, et al. Treatment of tularemia in pregnant woman. Fr Emerg Infect Dis U S. 2013;19:996–8.

43. Maurin M, Pelloux I, Brion JP, Del Bano J-N, Picard A. Human tularemia in France, 2006–2010. Clin Infect Dis U S. 2011;53:e133-41.

44. Johansson A, Berglund L, Sjöstedt A, Tärnvik A. Ciprofloxacin for treatment of tularemia. Clin Infect Dis U S. 2001;33:267–8.

45. Syrjala H, Schildt R, Raisainen S. In vitro susceptibility of *Francisella tularensis* to fluoroquinolones and treatment of tularemia with norfloxacin and ciprofloxacin. Eur J Clin Microbiol Infect Dis Ger. 1991;10:68–70.

46. Bloch-Infanger C, Furrer K, Wiese M, Hiebinger A, Bucher CM, Kopp S, et al. An unexpected cause for cavitary pneumonia and empyema. Infect Ger. 2016;44:539–41.

47. Celebi G, Baruonu F, Ayoglu F, Cinar F, Karadenizli A, Ugur MB, et al. Tularemia, a reemerging disease in northwest Turkey: epidemiological investigation and evaluation of treatment responses. Jpn J Infect Dis Jpn. 2006;59:229–34.

48. Passiouk N, Heininger U. Ulceroglandular tularemia following contact with a boar. Pediatr Infect Dis J U S. 2016;35:453–5.

49. Franco Hidalgo S, Prieto de Paula JM, Balaguer Zubieta I, Alvarez Ruiz AP. Infection due to *Francisella tularensis*, myocarditis and dilated myocardiopathy. Enferm Infecc Microbiol Clin. 2010;28:752–3.

50. Amort J, Karrer U. Zwei Fallbeispiele zur Tularämie: eine typische und eine atypische Verlaufsform. BAG Bull. 2013;(49/13):896

51. Gore I, Saphir O. myocarditis a classification of 1402 cases. Am Heart J. 1947;34(6):827–30.

52. Saphir O. Myocarditis A general review, with an analysis of two hundred an forty cases. Arch Pathol. 1941. https://doi.org/10.1179/nhi.1988.24.1.227.

53. Saphir O. Isolated myocarditis. Am Heart J. 1942;24:167–81.

54. Aaagard GN. Involvement of the heart in tularemia. Minn Med. 1944;27:115–21

55. Miller J. Granulomatous myocarditis. A case for diagnosis. Can Med Assoc J. 1933;29:134–7.

56. Ilback NG, Friman G, Beisel WR, Johnson AJ. Sequential metabolic alterations in the myocardium during influenza and tularemia in mice. Infect Immun. 1984;45:491–7.