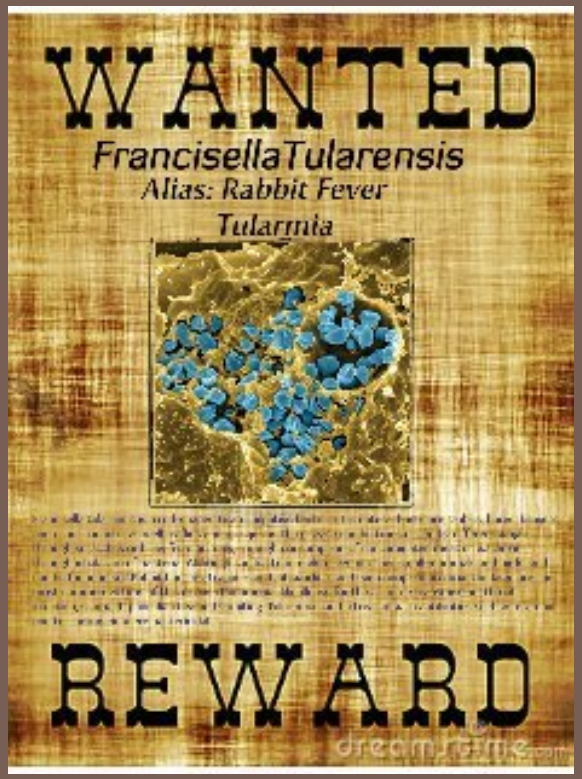


RESURGENCE OF *F. TULARENSIS* IN BELGIUM ?

Dr. B. DELAERE, Erasme, dec 2015

CHU Dinant Godinne
UCL NAMUR

Case report 1 (2012)

Healthy 25-year-old man, student LLN

- ✓ Travel in south of France (holidays) 6 months ago, not pets, play tennis.
- ✓ 3weeks ago: fever, myalgia, fatigue. Amox-Clav by GP, without improvement.
- ✓ Bilateral conjonctivitis followed by a painful disseminated acneiform rash (arms, legs, buttocks, thorax and the face including the scalp).
- ✓ Febrile with night sweats, moderate altereted status.
- ✓ Doxycycline (3d) prescribed by the GP due to the extension of the cutaneous lesions ➔ ID consultation

Case report 1:

Healthy 25-year-old man, student LLN, ID consultation

- ✓ Arthralgia (knees, ankles, elbows) with fonctionnel disability
- ✓ Decreasing rash and fever
- ✓ Right axillair-anterior painful lesion with local erythema.
- ✓ Remains an injury on his right index during hunting, later handled a dead wild boar.
  - Suppurative lesion: Clonazone with a slow recovery.

Case report 1:

Healthy 25-year-old man, student LLN, ID consultation

- Physical examination: no fever, diffuse crusty healing cutaneous lesions and purple non-suppurative lesion on the right index finger.

- An inflammatory (3x5cm), erythematous and painful adenopathy on the anterior area of the axillar region.

- Biology: elevated CRP (94mg/l), WBC count of $10.9x10^3/\mu l$ (66%PNL, 11% monocytes) with a normal platelet count.

Case report 1:

Healthy 25-year-old man, student LLN, ID consultation

- ✓ Doxycycline extended for 14 days, pending results for serology.
- ✓ Diagnosis confirmed by an ELISA (CERVA)
- ✓ Improvement with complete defervescence within the week, complete resolution of cutaneous lesions and decreasing of volume and inflammation of the adenopathy.
- ✓ 4 weeks later, recurrence of symptoms. Ciprofloxacin 750 mg bid for 21 days (skin fistula).

Case report 2 (2015)

68 years-old woman

ID consultation

- ✓ C2H5 abuse, no medication
- ✓ Altered status, mild recurrent fever and night sweats, fatigue, anorexia for 3 weeks.
- ✓ Index lesion « panari »: clonazone, staphycid/amox-clav, surgical debridement
- ✓ 2 subcutaneous painful nodules on the forearm
- ✓ 3 inflammatory painful adenopathies at elbow (2-2-1cm), one axillary (4cm)
- ✓ Elevated CRP and leucocytosis.

Case report 2 (2015)

65 years-old woman, pensionnée

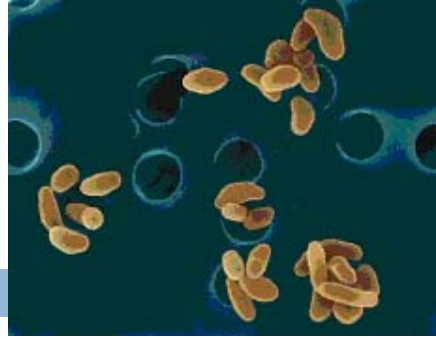
ID consultation

- ✓ 4 weeks ago, got an index wound during gardening
  - ✓ garden plowed by wild boars (Wépion)
- ✓ Cutaneous nodule biopsy
- ✓ Clinical suspicion, confirmed by serology
  - ✓ Biopsy: non necrotizing granulomatous lesion
- ✓ Ciprofloxacin 3 weeks, with improvment
  - ✓ Recurrence 3 weeks after cessation of AB (axillar adenopathy)
    - ✓ New treatment of 3 weeks, no recurrence

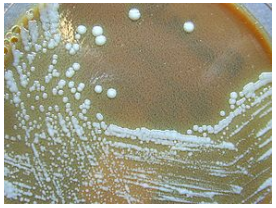
2 others cases (2013-2014)

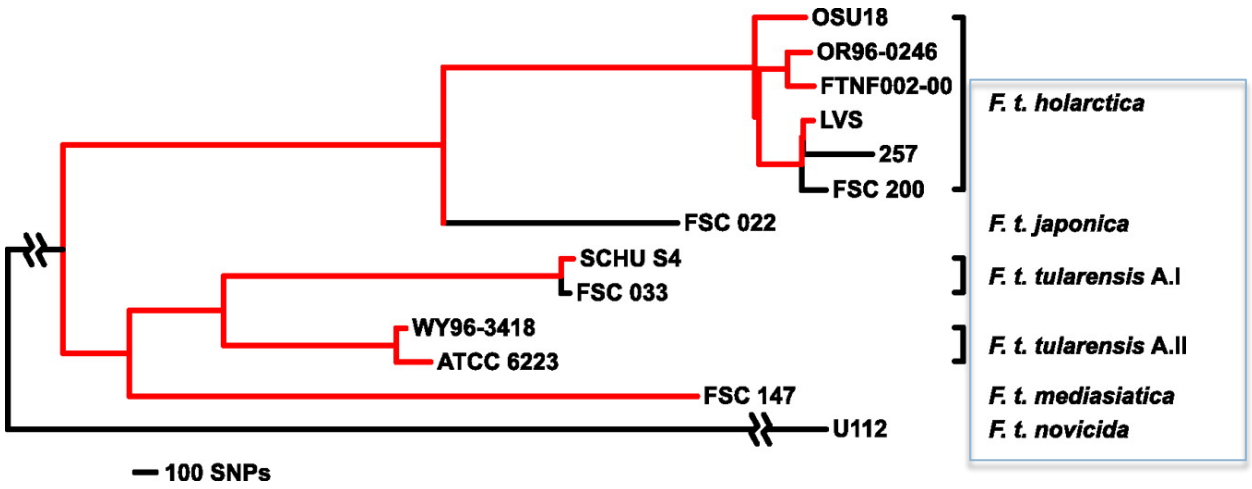
- ✓ 39-years-old farmer, hunter
  - Ulcero-glandular presentation
  - Bite on the knee, cutaneous lesion
  - Inguinal adenopathy, general malaise with fever
  - 2 weeks of doxy
- ✓ 30-years-old man, trailer
  - Ulcero-glandular presentation (inguinal adenopathy)
  - Wound on the left knee, cutaneous chronic lesion
  - General malaise with fever
  - 3 weeks ciprofloxacin
    - acneiform/maculo-papulous eruption at d1

F. tularensis: Microbiology



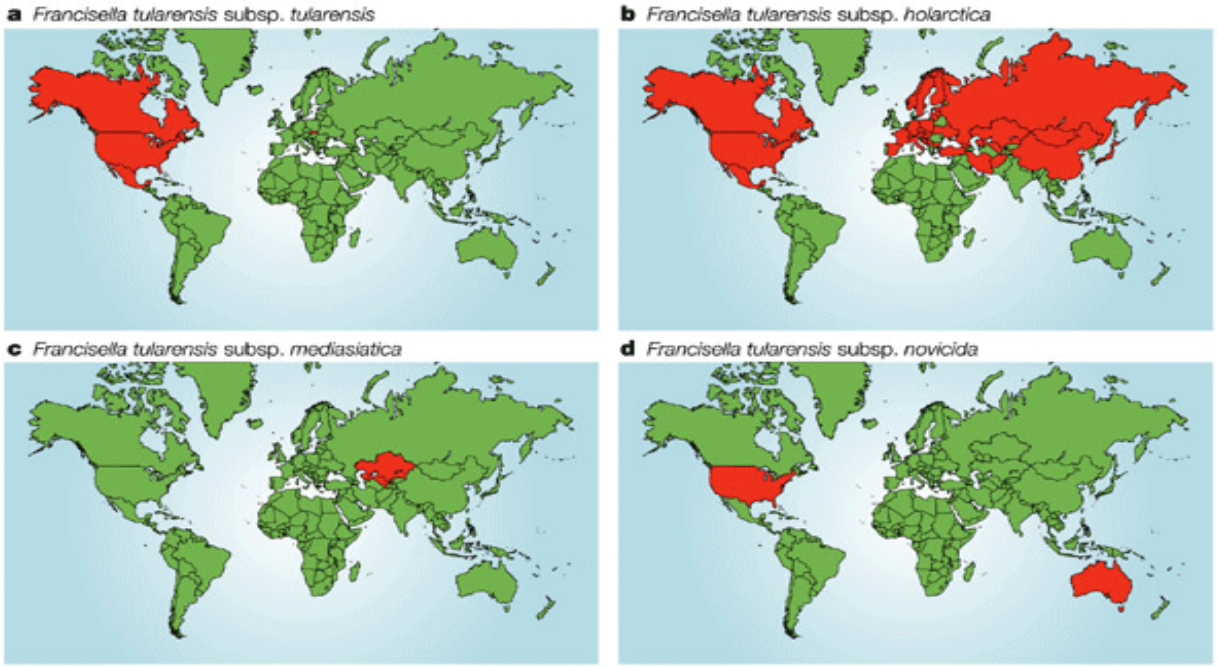
- ✓ Facultative intracellular bacterium
  - Aerobic Gram-negative cocco-bacilli
- ✓ Family Francisellaceae
  - 2 species in the genus *Francisella*
    - ✓ 4 subspecies of *F. tularensis: tularensis, holarctica, novicida, mediasiatica*





F. tularensis: Phylogenia

- ✓ *F. tularensis* and *holarctica*:
  - Main subspecies associated with human diseases
    - *F.T. tularensis*: most virulent, mainly described in North america
    - F.T. *holarctica*: less virulent, is predominantly found in Asia and in Europe(but also in North America)



Nature Rev Microbiol 2004, Petra

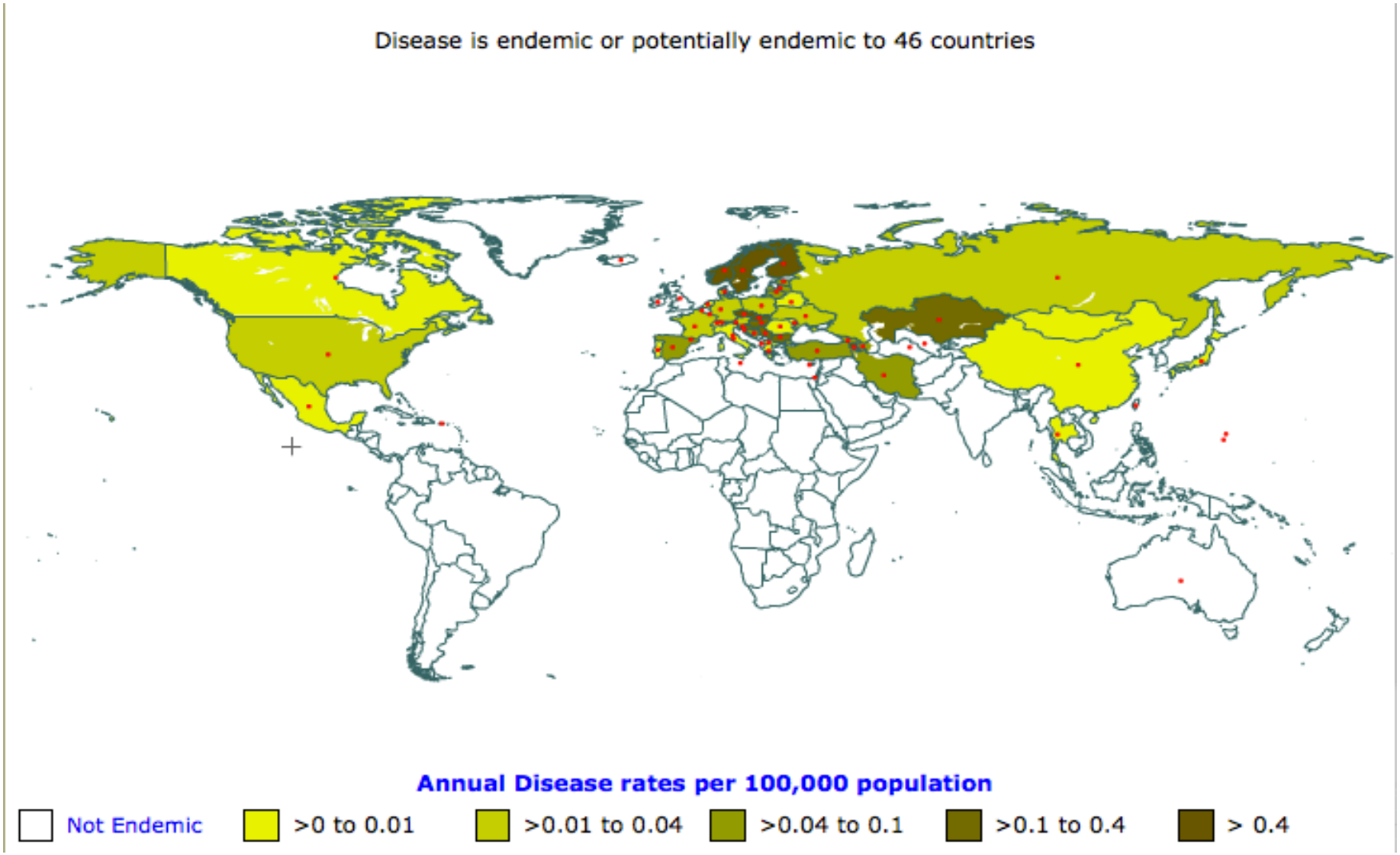
F. tularensis: *Epidemiology*

- Firstly described in the County of Tulare, California,
  - by McCoy and Chapin in ground squirrel with a plague-like illness (1911)
  - then isolated and cultivated by Dr. Edward ***Francis*** (1919)
- Reservoirs:
  - Infect hundred of different vertebrates and invertebrates
  - no more than dozen mamalian species are important to its ecology
    - predominently lagomorphs and rodents (voles, squirrels, muskrats, hares, ...).
  - bloodfeeding arthropods and flies are also important vectors for animals and human diseases.

F. tularensis: Epidemiology

- ✓ In Europe, endemic foci vary significantly
  - Scandinavian countries report high number of cases annually (Sweden, Finland)
  - Fewer cases are reported in central and southern Europe (France, Hungary, Austria, Czech republic, Germany, Spain)
- ✓ It re-emerged in the early 21th century
  - in Turkey, Bulgaria, Kosovo, Georgia
  - with many outbreaks reported (France, …)
- ✓ in Belgium since 1950
  - ✓ only 3 other cases were reported
    - ✓ data from Coda-cerva, only one clinical report
  - ✓ 4 cases in CHU between 2012-2015
- ✓ Agent of bioterrorism

F. tularensis: Epidemiology

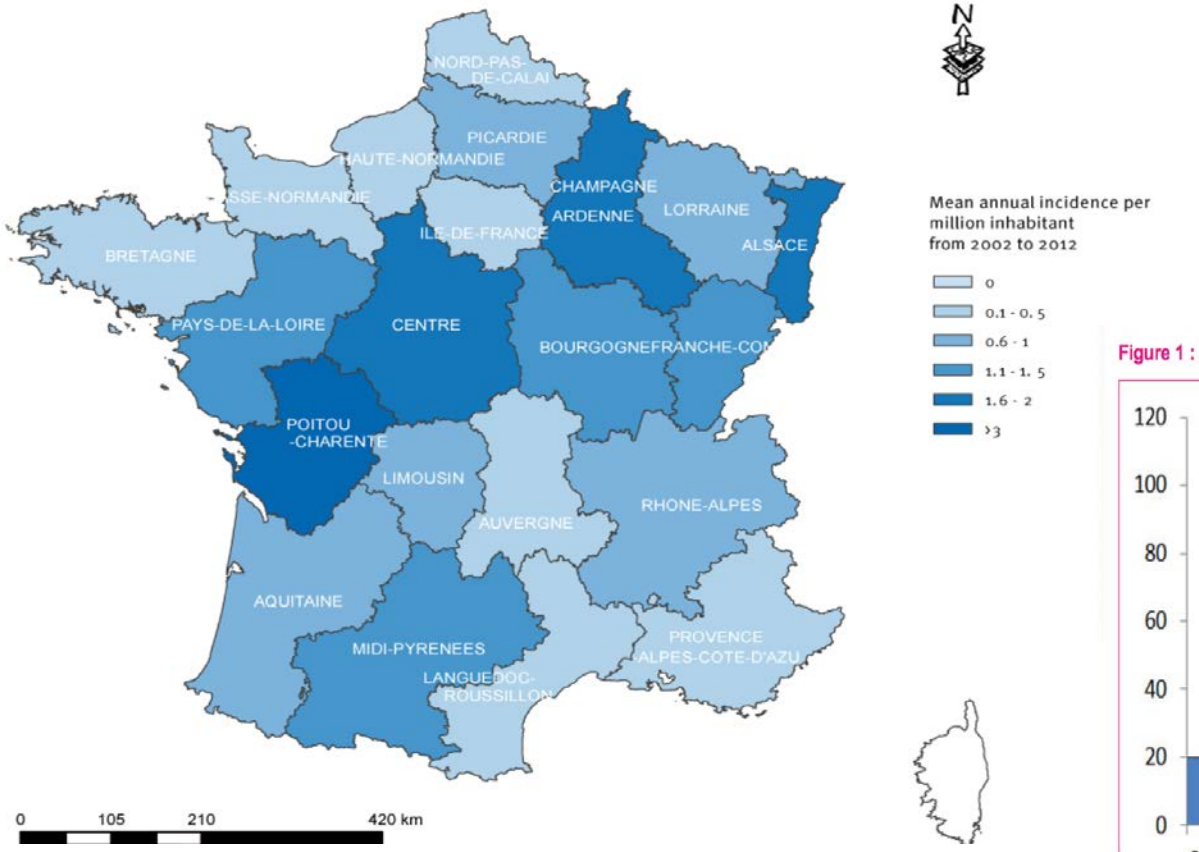


ECDC

F. tularensis: Epidemiology

FIGURE 3

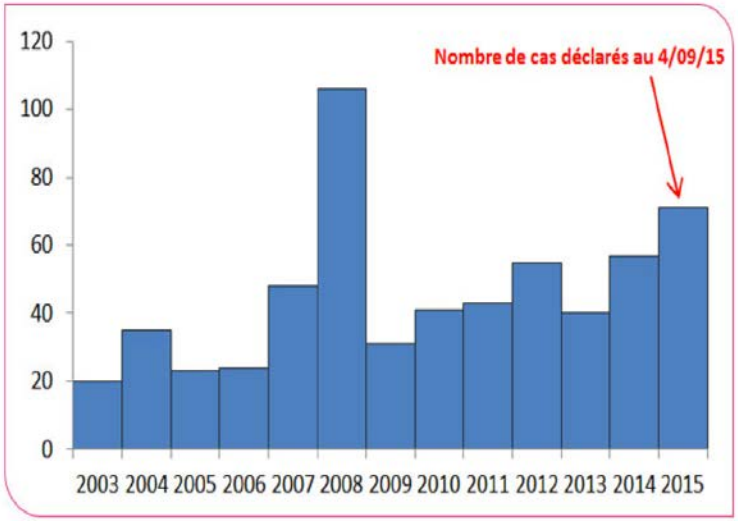
Incidence of tularemia by region of residence of the cases, France 2002-2012



Euro Surveill. 2014;19(45):pii=20956.

INVS sept2015

Figure 1 : Nombre de cas de tularémie par date de déclaration, France 2003-2015



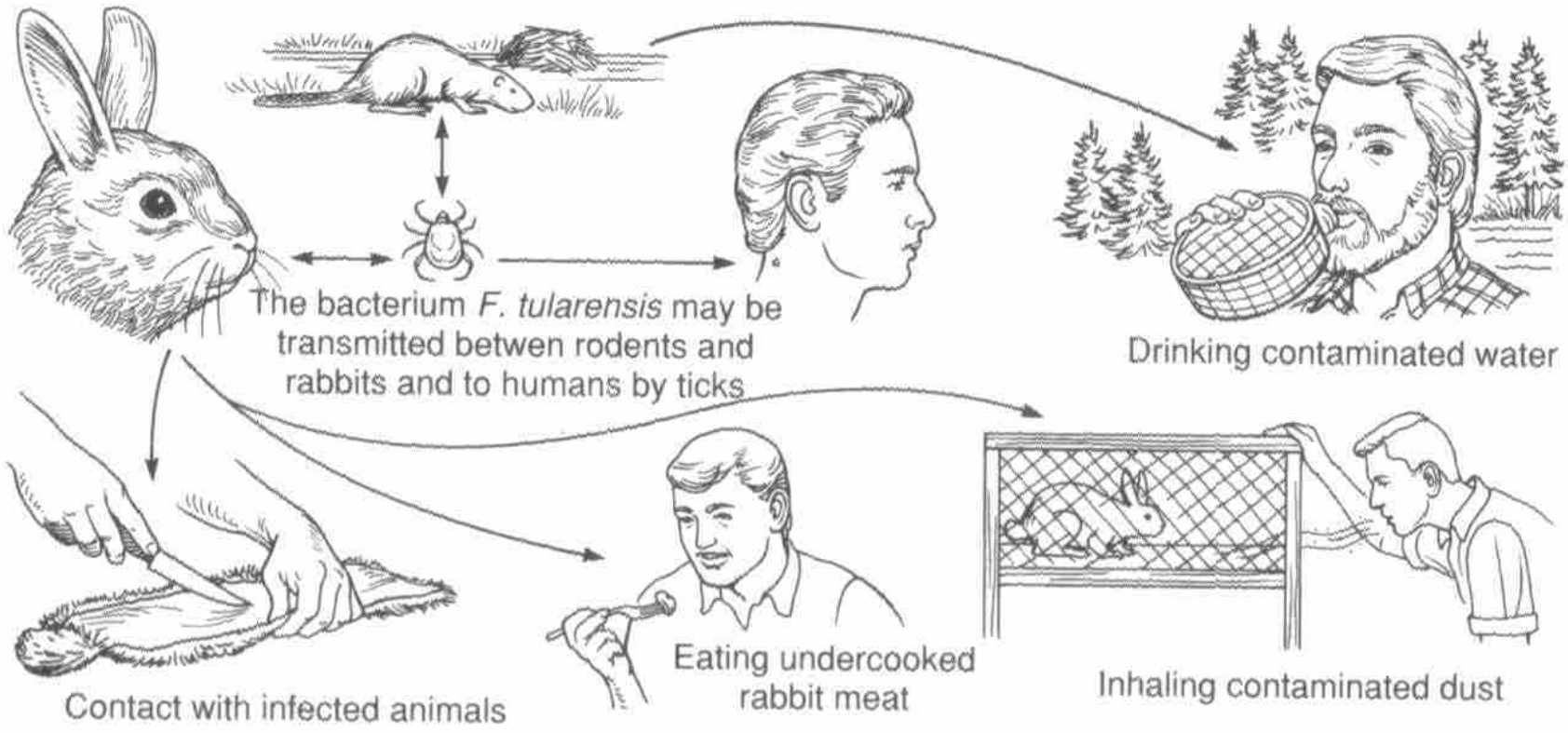
F. tularensis: Pathogeny

- ✓ Survives few days in the environment if over 10°c
  - but many months in water, mud, straw, … below 0°c.
- ✓ Infectious dose in human depends on the portal of entry (and subsp.):
  - 10-50 organisms intradermally or when inhalated
  - 10^8 organisms when ingested
- ✓ Penetration:
  - mainly through sites of inapparent skin disruption
  - reported to penetrate intact skin

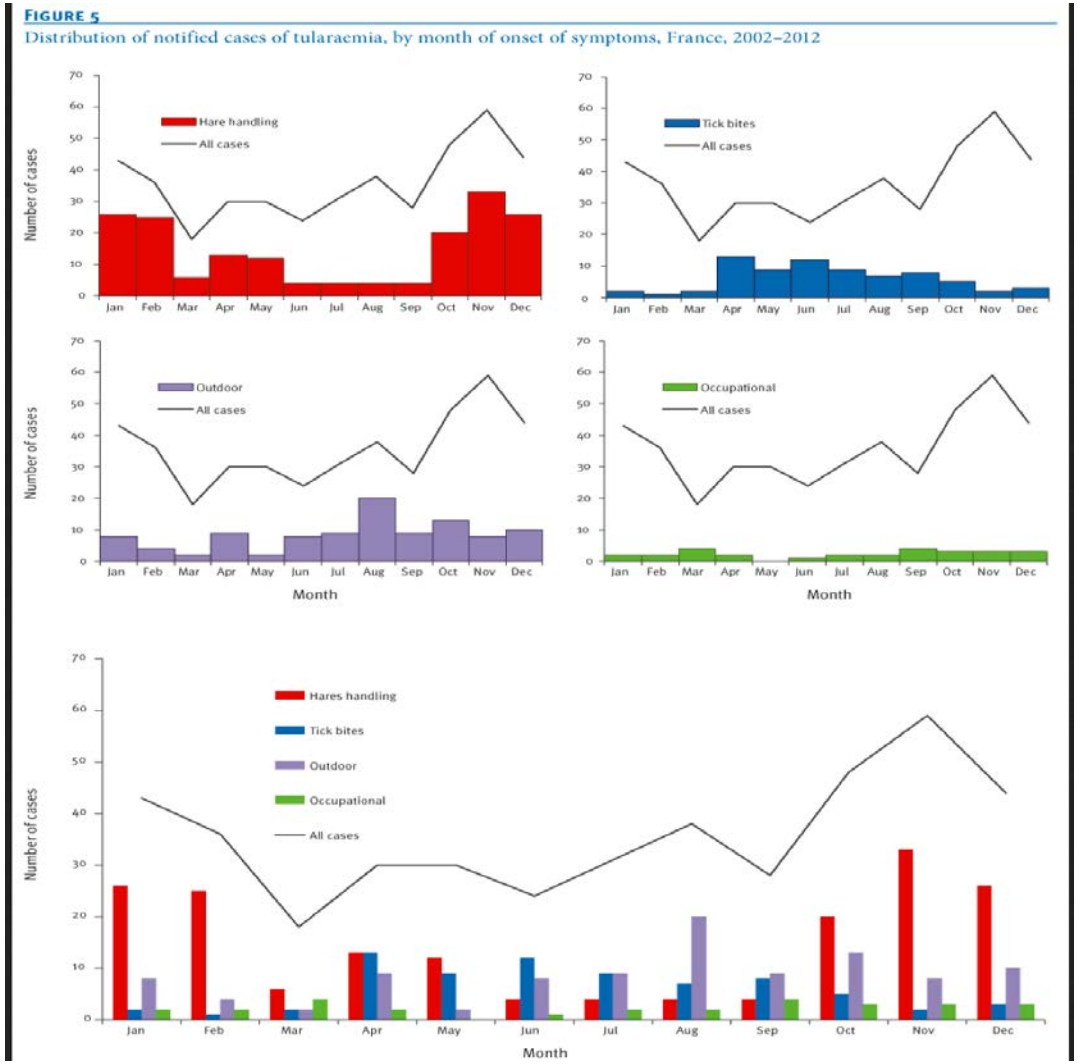
F. tularensis: Pathogeny

Tularemia (tu-lar-e′me-a) Tulare county, California where discovered 241

DEFINITION: An acute, infectious disease of wild rabbits and rodents caused by the bacterium, *Francisella tularensis;* also known as *rabbit fever.*



F. tularensis: Epidemiology



Euro Surveill. 2014;19(45):pii=20956.

F. tularensis: Clinical disease

- ✓ Depends on
  - the virulence of the strain
  - the portal of entry
  - the extent of systemic involvment
  - the immune status of the host

  ➔from asymptomatic to acute sepsis and death (rare *F. t. holartica*)
- ✓ Incubation period: 3-5 days (vary from 1 to 21 days)
- ✓ Systemic symptoms
  - start abruptly: fever, chills, headache (flu-like sdo)
  - less virulent strains cause a milder, self-limited disease that may resolve without therapy.

F. tularensis: Clinical disease

- ✓ 6 classic forms of tularemia, with some overlaps in many patients
  - Ulcero-glandular tularemia
  - Glandular tularemia
  - Oculo-glandular form
  - Oropharyngeal disease
  - Pulmonary tularemia
  - Systemic disease: typhoidal tularemia

F. tularensis: Ulcero-glandular disease

- ✓ Most common form in central Europe
- ✓ After a cutaneous inoculation, *F. tularensis* multiply localy and produces a papule
  - ➔2-4 days later ulceration ➔spread to regional lymph nodes ➔ lymphohematogen dissemination
- ✓ The skin lesion may appear before, simultaneuosly with or several days after the adenopathy.
  - skin lesion and adenopathy are painful
  - If untreated, ulceration may take weeks to heal in a residual escar and adenopathy can become fluctuant or fistulated
  - Location of the ulcer generally reflects the mode of contamination:
    - hands and forearms: animals or environmental contact
    - trunk, lower extremities, head and neck: suggests insects bites

F. tularensis: Other glandular diseases

- ✓ Glandular disease: the 2d most common
  - but the first in children
  - with single or multiple adenopathy without skin lesion
  - mode of acquisition is similar than ulcero-glandular disease.

- ✓ Oculoglandular presentation:
  - occurs when *F. tularensis* gains access to the conjunctiva
  - symptoms includes conjunctivitis with regional adenopathy (*Parinaud's oculoglandular syndrome*)

F. tularensis: Oropharyngeal disease

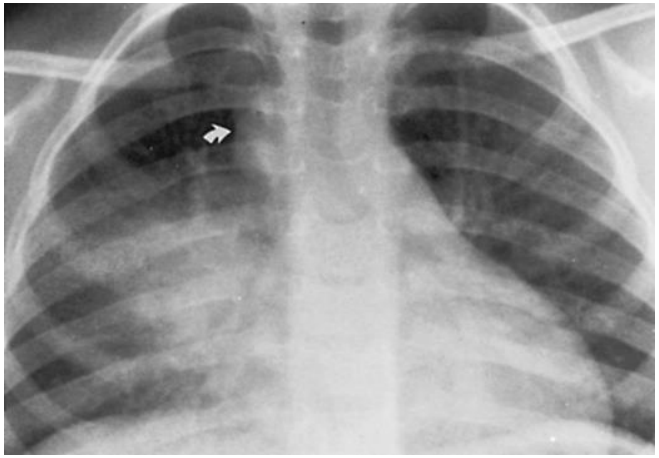
- ✓ Oropharyngeal disease is rare in USA/central europe
  - frequently reported in outbreaks in some countries
    - Kosovo, Turkey
  - following ingestion of contaminated food or water,
  - fever and severe sore throat with exsudative tonsillitis or pharyngitis (frequently ulcerated) and cervical lymphadenopathies

F. tularensis: Typhoidal tularemia

- 5-30% of cases
  - is a febril illness without regional adenopathy or others localizing signs.
  - the most difficult to diagnose
    - clinical presentation ranging from acute sepsis to chronic illness.
    - chronic underlying conditions are frequently reported.
    - it can results of any portal of entry.
  - Major symptoms:
    - high and prolonged fever, headache, myalgia, sore throat, anorexia.
    - **Diarrhea**, a major manifestation only in typhoidal tularemia
      - watery and loose.
    - Secondary pulmonar involvment is reported in up to 45% of cases

F. tularensis: Pulmonar disease

- ✓ More common in adults patients (up to 25% of cases)
  - It results from direct inhalation of the bacteria or from secondary hematogenous spread to the lung.
  - Pneumonia due to *F. tularensis subsp. tularensis* is more severe than that caused by *subsp. holarctica*, but disease may be prolonged in both cases



F. tularensis: Secondary manifestations

- ✓ Secondary skin manifestation: frequent ≈30%
  - many forms such as
    - maculo-papular or vesiculo-papular eruption,
    - erythema multiforme *(typhoidal tularemia)*,
    - pustules, acneiform lesions, urticaria,
    - erythema nodosum *(most commonly with pneumonic tularemia, typhoidal tularemia)*,
    - sweet syndrom
  - usually appearing within the first 2 weeks of symptoms

F. tularensis: Diagnosis

- ✓ Based on **clinical suspicion** with epidemiological history
- ✓ Routine lab tests are non specific
- ✓ Microbio lab:
  - rarely seen in Gram stained smear or tissue biopsy
  - does not grow in routinely plated culture
  - can be recovered from any liquid of tissue if processed in supportive media
  - *high virulence and transmissibility*: a biosafety level 3 is required to process isolates suspected of being infected

F. tularensis: diagnosis

- ✓ Serology: most common way to the diagnosis *(Coda-cerva)*
  - Agglutination, microagglutination, ELISA (*F. t. tularensis/holarctica)*
  - Usually negative the 1rst week of symptoms but (+) in most patients after 2 weeks and peak after 4-5 weeks.
    - A presumative diagnosis: an acute agglutination titer of ≥1/160 or an acute microagglutination ≥1/128.
    - IgM and IgG appear together and high titers may persist for long time.
      - Definitive diagnosis ≥4x in titer between acute and convalescent serologies (10 days).
    - Cross reactions is reported with *Brucella sp, Yersinia sp* and *Proteus OX19*
- ✓ PCR: Not commonly available
  - Coda-cerva, subtypes identification

F. tularensis: Treatment

- Streptomycin 7,5-10 mg /kg/12h IM (adult, up to 2g/d)
  - Excepted in meningitis
  - High rate of cure, low rates of relapses
  - Gentamicin od (3 à 5 mg/k, peak ≥5,0 µg/ml) as alternative
  - 7-10 days, up to 14d in more severe case or if response to treatment is delayed
- Chloramphenicol is effective
- Tetracyclines is an alternative, but 14d required and *more relapses* reported (up to 15%) (doxy 200mg/d)

F. tularensis: Treatment

- ✓ Good in vitro susceptibility to fluoroquinolone
  - *subsp. holarctica* (few data available for *tularensis subsp.*)
  - considered by some as the drug of choice in mild or moderate tularemia
    - for at least 10-14 days
    - Some relapses

F. tularensis: Resurgence ?

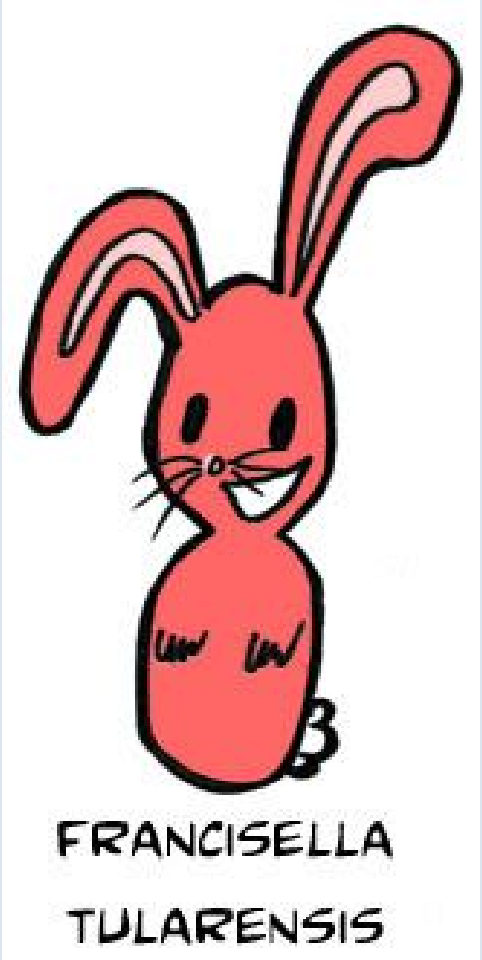
- ✓ Many european countries published a increasing number of cases, including in non endemic aeras
- ✓ Increasing incidence possibly related to:
  - Expansion of the animal reservoir (rabbits, rodents),climat change ?
  - importation of infected game animal from Eastern Europe
  - Arthropod vectors proliferation (ticks) ?
  - More frequent contact with the natural reservoirs during outdoor activities ?
  - Water/food contamination (Turquey)
  - Combination of these factors
  - More reported ?

F. tularensis: Resurgence ?

- ✓ Only 3 cases diagnosed in Belgium since 1950 …
  - 4 cases in 3 years at MontGodinne (+1)
  - Underdiagnosed disease in higher risk area ?

- ✓ Diagnosis has to be evocated
  - Febrile illness with adenopathy +/- skin lesion, +/- eruption
  - With an incubation period of 3-5d, non responding to classical antibiotic
  - With epidemiological risk factors
    - outdoor activities, hunting, tick bites

- ✓ Human surveillance and evaluation of animal reservoir



MERCI DE VOTRE ATTENTION