

## Q FEVER

Prevention and treatment issues  
during an outbreak

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## *Q fever outbreak, what to do?*

### Based on literature:

- Diagnosis of acute Q fever based on serology
- Echocardiography performed in every patient
- Serological follow up every 3 month for 1 year

### Problems:

Workload, echo cor after acute Q not necessary in NL-population

[Limonard, Lancet infection disease, 2011](#)

High work-load serological follow up, after evaluation:

No risk factors present for chronic Q fever (cardiac valves problems, vascular stents, aneurysmata, pregnancy, immunodeficiency):

Follow up after 9 month

Risk factors present for chronic Q fever:

Follow up every 3 month for 1 year

Diagnostic delay in the early stage of the disease: Need for PCR

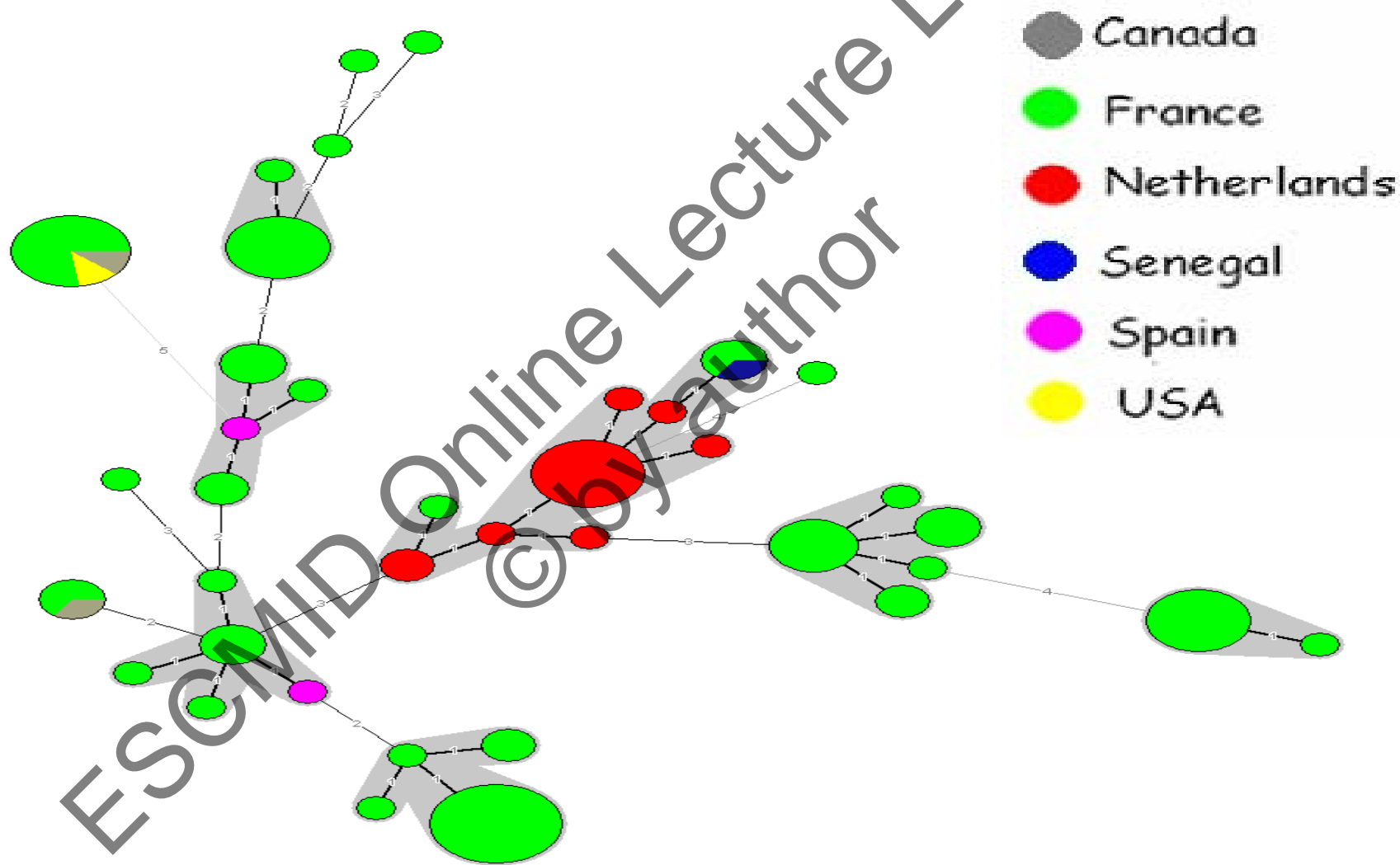
# Q fever outbreak, what is the source???

## MST analysis

- closely related genotypes in human and animal samples from outbreaks throughout the NL which confirms clonal origin
- With MLVA similar findings

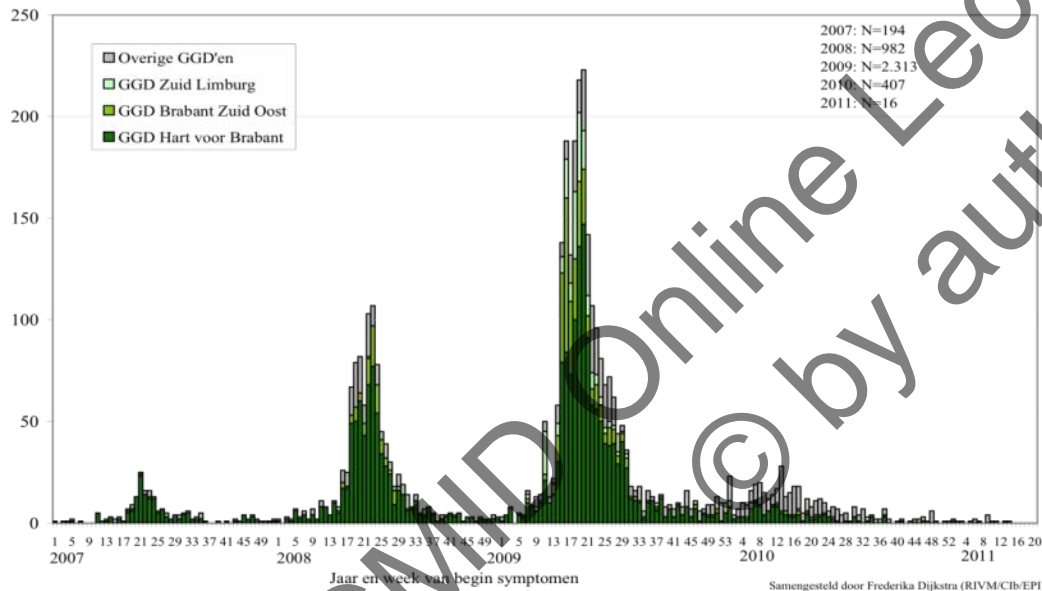


*Q fever outbreak, what is the source???*



# Legislation Q fever in the NL

Aantal gemelde Q-koorts-patiënten met bekende 1e ziektedag naar week van begin symptomen.  
Periode: 01-01-2007 tot 27-04-2011.



## Small ruminants Goats and Sheep

- Notifiable disease
- Ban of spread manure
- Strict hygiene measures
- Bulk tank milk monitoring (every 2 months)
- Transport ban animals Q+ farms
- Visitors ban Q+ farms
- Reproduction ban of goats
- **Vaccination**
- Bulk tank milk monitoring (every 2 weeks)
- Measures removing and storing manure
- **Culling pregnant animals**

# Q fever - clinical picture

2007

Asymptomatic (60%)

Symptomatic (40%)

Mild (20%)

Fever, flu like symptoms

Moderate (15%)

Severe (5%)

Hospitalization 2-5%  
Pneumonia  
Hepatitis

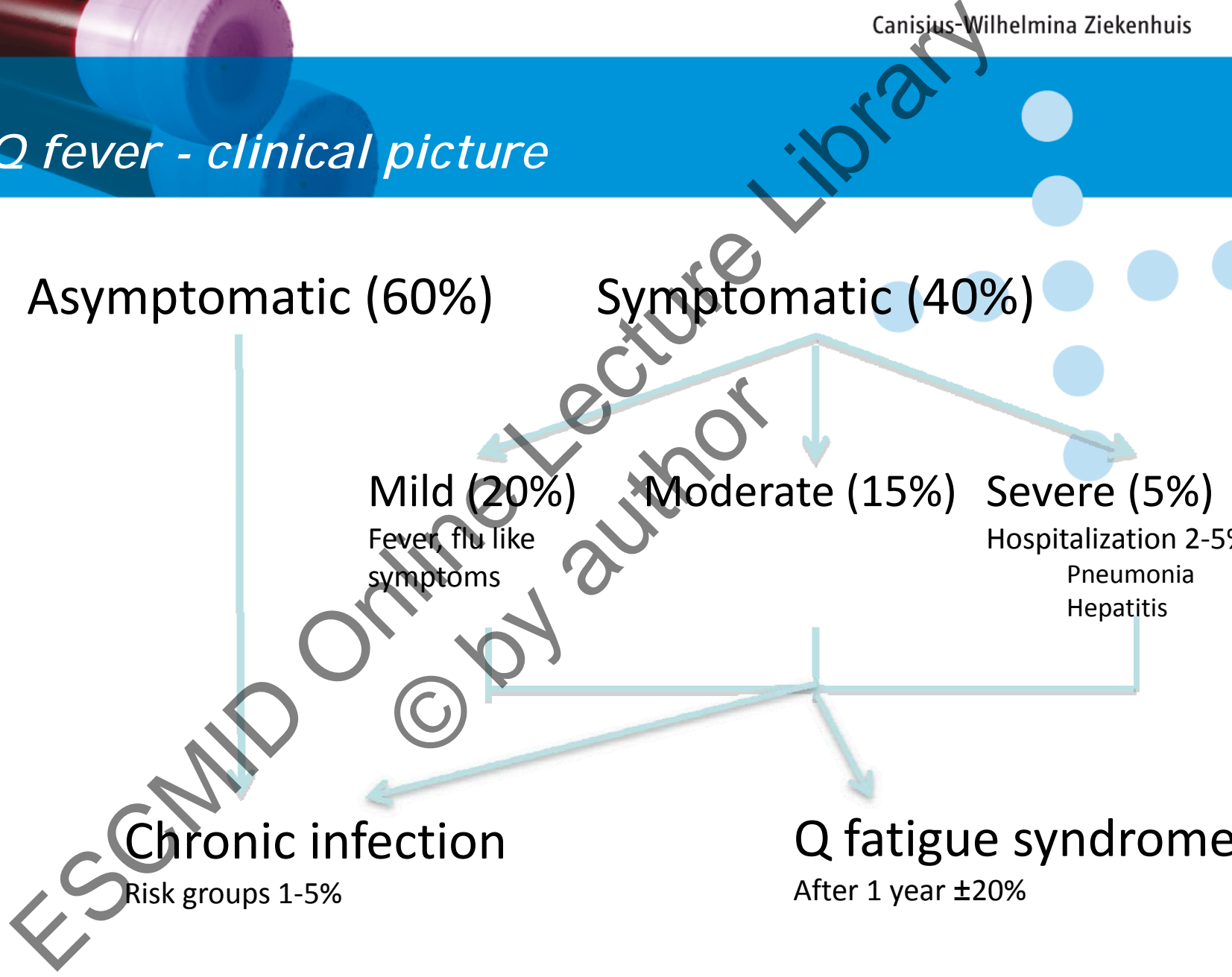
2010

Chronic infection

Risk groups 1-5%

Q fatigue syndrome

After 1 year  $\pm$ 20%

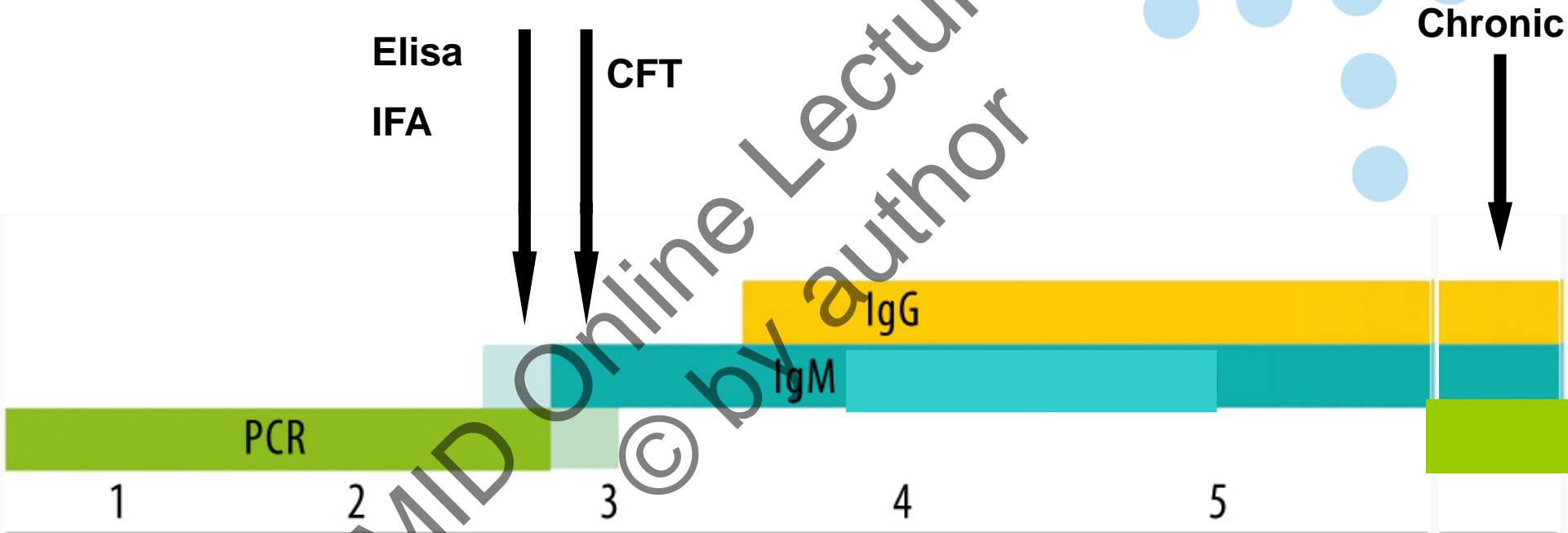


# *Acute Q fever*

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# Acute Q fever - diagnostics



Dutch Consensus group, NtvG, 2010



# Acute Q fever - diagnostics - PCR

JOURNAL OF CLINICAL MICROBIOLOGY, Nov 2010, p. 3423-3427  
 0095-1137/10/\$12.00 doi:10.1128/JCM.01006-10  
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## Interlaboratory Evaluation of Different Extraction and Real-Time PCR Methods for Detection of *Coxiella burnetii* DNA in Serum<sup>7</sup>

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In the Netherlands, there is an ongoing and uncontrolled outbreak of Q fever. Rapid and reliable methods to identify patients infected with *Coxiella burnetii*, the causative agent of Q fever, are urgently needed. We evaluated the performance of different DNA extraction methods and real-time PCR assays that are in use in seven diagnostic or reference laboratories in the Netherlands. A low degree of variation in the sensitivities of most of the developed real-time PCR assays was observed. However, PCR assays amplifying short DNA fragments yielded better results than those producing large DNA fragments. With regard to DNA extraction, the automated MagNA Pure Compact system and the manual QIAamp DNA mini kit consistently yielded better results than either the MagNA Pure LC

## Acute Q fever - treatment NL

### Acute Q fever:

- 1<sup>e</sup> : Doxycycline 200 mg 1 dd, 14 - 21 days  
2<sup>e</sup> : Moxifloxacin 400 mg 1dd, 14 days

### Pregnancy:

- 1<sup>e</sup> 2<sup>o</sup> trim.: Trimeth.-sulfa. 160 mg/800 mg 2 dd  
3<sup>e</sup> trim.: Erythromycine + rifampicine

### Children < 8 yrs:

- 1<sup>e</sup> : Trimeth.-sulfa. 3/15 mg/kg 2 dd, max. 320/1600 mg  
2<sup>e</sup> : Clarithromycine 15 mg/kg, max 1000 mg, in 2 doses

## Acute Q fever - Pregnancy

- transmission described during delivery is described
  - [Riechman, Am J Med, 1988, 253-4](#), [Stein, Clin infect dis, 1998, 592-6](#)
  - [Raoult, N Engl J Med, 1994, 371](#)
- Measurements during delivery:
  - Strict droplet and contact isolation
  - Contaminated materials should be removed carefully
  - Room should be ventilated and cleaned
  - In NL: antimicrobial prophylaxis is not given to persons present during delivery
- Breast feeding:
  - Transmission between mother - child is possible
    - [Raoult, Arch intern med, 2002, 701-4](#)
  - do NOT give breast feeding (ECDC)
  - NL: it depends on the results of pcr tests on birth-product and milk
  - When PCR's neg and patient was treated during pregnancy  $\geq 5$  weeks, breast feeding is allowed.

# Acute Q fever - Information for public

## Public information campaigns

- About the disease
  - Symptoms
- About prevention
  - Consumption of
  - Contact with
  - Target zones of increased risk
- About "self management"
  - Take care to
  - Be aware of

## Information for sector / professionals

- [www.rijksoverheid.nl](http://www.rijksoverheid.nl)
- [rivm.nl](http://rivm.nl)
- [lci.nl](http://lci.nl)
- [kiza.nl](http://kiza.nl)

Professional organizations



## *Acute Q fever - Blood and tissue-donations*

- Blood donations:
  - Transmission by donated blood is rare
  - NL: all donated blood from high risk areas are tested (PCR) for presence bacterial DNA
- Tissue donation:
  - No data about transmissions available
  - Better sure than sorry: PCR
- Sperma donation:
  - In literature: 1 probable case of transmission described
  - In nl: 1 patient with orchitis and high DNA load in sperma
  - Nationale health authoraties will decide if PCR screening is necessary

# Q fever - chronic problems

2007

Asymptomatic (60%)

Symptomatic (40%)

Mild (20%)

Fever, flu like symptoms

Moderate (15%)

Severe (5%)

Hospitalization 2-5%  
Pneumonia  
Hepatitis

2010

Chronic infection

Risk groups 1-5%

Q fatigue syndrome

After 1 year  $\pm$ 20%

## Chronic Q fever

### Dutch consensus

#### Diagnosis for Chronic Q is based on:

1. risk factors for chronic Q fever
2. clinical symptoms
3. laboratory tests results (pcr, serology: IgG 1  $\geq$  1024 )
4. Imaging results (X-ray, MRI, PET-CT)

#### Classification:

Proven

(positive PCR, IgG 1  $\geq$  1024,  
pos dukes criteria for endocarditis or pos imaging  
for aneurysm)

Probable

Possible

## Chronic Q fever - screening

- In NL an increasing numbers of chronic Q cases is diagnosed
- Without acute Q fever in history
  - With infected vascular prostheses AAAA → high mortality!!

This was the reason for screening of all patients in the high risk area with:

- Cardiac valve prostheses
- Vascular prostheses / stents
- Known aneurysms



Seroprevalence between 10 - 20%

Chronic patients 2 %



## *Chronic Q fever - screening*

- If screening is positive:
  - Classification following Dutch consensus on chronic Q fever (proven, probable, possible)
- If treatment is necessary:
  - Start of treatment before symptoms become present
  - Until now, good clinical outcome (1 patient with an abdominal aneurysm became negative in serology and imaging)
- Problems longterm treatment:
  - Side effects of the medication

# Chronic Q fever - clinical picture

## Literature

Endocarditis 78%  
 Vascular disease 9%  
 Chronic infection after pregnancy 5%

### Other

- Chronic hepatitis
- Chronic pneumonia
- Meningo-encephlitis
- osteomyelitis

## The Netherlands

Endocarditis 70%  
 Vascular disease 30%  
 Chronic infection after pregnancy 1 patient

### Other

- Chronic hepatitis
- Chronic pneumonia
- Meningo-encephlitis
- osteomyelitis

## Chronic Q fever - treatment

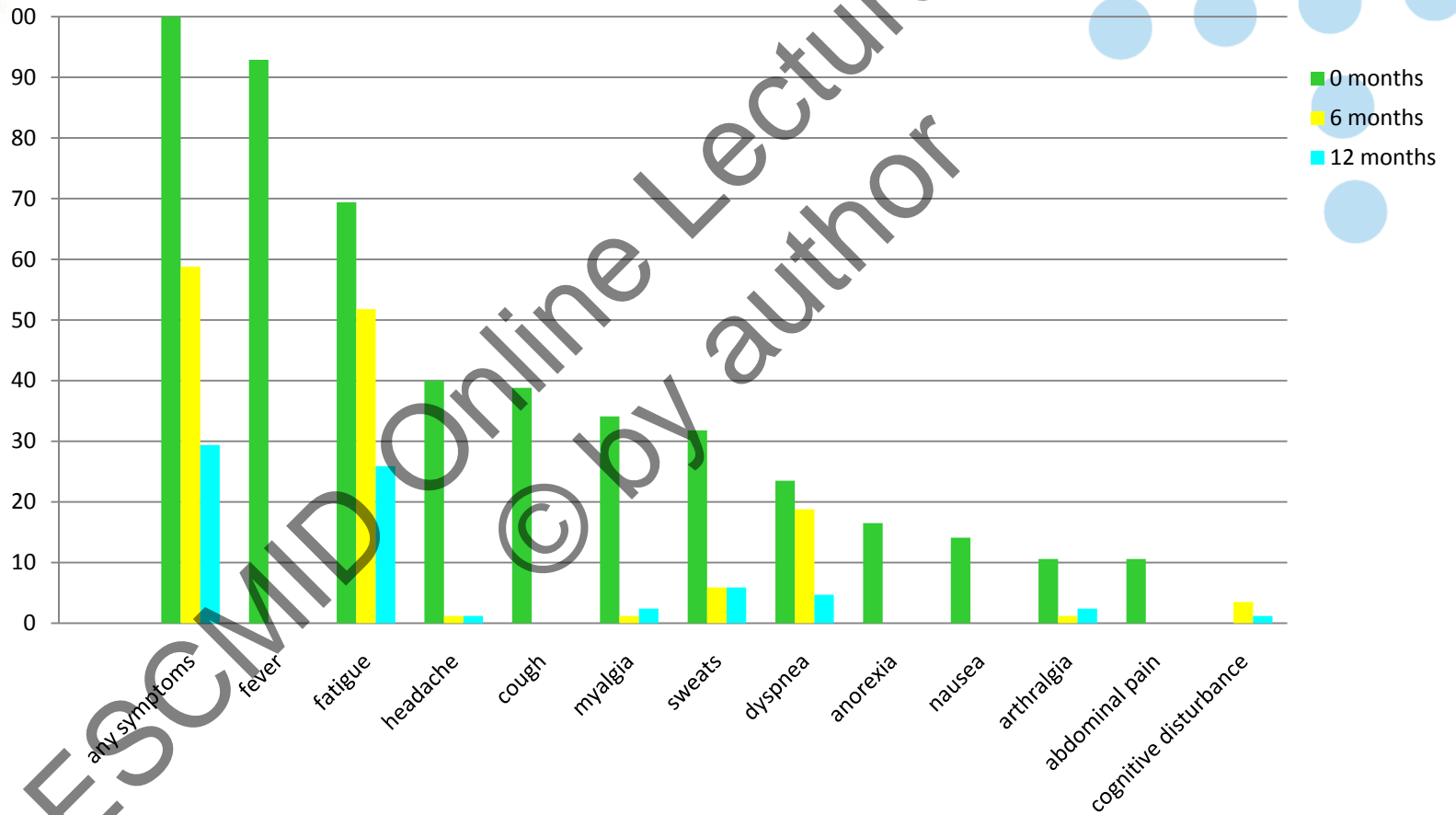
### Treatment

- 1e :      doxycycline 100 mg 2 dd, serumlevels: > 5 mg/L +  
            hydroxychloroquine 200 mg 3 dd, serumlevels: 0.8 - 1.2 mg/L
- 2e:      Quinolone + Rifampicine

### Background

- *C. Burnetii* in phagolysosome at a pH 4.5
- Optimal pH for antibacterial activity of doxycycline at pH 6.6
- Hydroxychloroquine increases pH in phagolysosome from pH 4.5 to pH 5.7, which improves activity doxycycline

# Chronic fatigue syndrome



## *Chronic fatigue syndrome*

In the Herpen Cohort, the fatigue scores of the cohort patients measured 12 month after primary Q fever were significantly elevated compared to controls (P=0.004)

## *Challenges for the future*

1. To improve diagnosis and treatment of acute Q - fever
1. To improve (early) diagnosis and treatment of chronic Q-fever (Susceptibility testing)

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Proven chronic Q fever

- a. Positive *C. burnetii* PCR in tissue and/or blood in the absence of acute Q fever
- b. IFA Phase I IgG titer  $\geq 1:1024$  with evidence of endocardial involvement according to the Duke criteria:
  1. Positive echocardiogram for Infective endocarditis (IE) defined as:
    - oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation, or
    - abscess, or
    - new partial dehiscence of prosthetic valveor
  2. New valvular regurgitation (worsening or changing of preexisting murmur not sufficient)
- c. IFA Phase I IgG titer  $\geq 1:1024$  and signs of vascular infection on PET-CT, CT or ultrasound.

## Probable chronic Q fever

IFA Phase I IgG titer  $\geq 1:1024$  together with:

- a. Cardiac valvulopathy (previously unknown) or worsening of valvular function not meeting the criteria for endocardial involvement according to the Duke criteria
- b. Aneurysm, vascular prosthesis or cardiac prosthetic valve, without signs of infection on TEE, PET-CT, CT or ultrasound.
- c. Signs of possible chronic Q fever infection of non-cardiac or vascular origin on PET-CT, CT or ultrasound (for example hepatitis, osteomyelitis)
- e. pregnancy
- f. Clinical symptoms of chronic infection like fever, weight loss, night sweats, glomerulonephritis, hepatitis (ik dacht dat die er juist wel in bleef)
- g. pathological proven granulomatous inflammation of tissue
- h. immune disorder as described in this document

Advice: refer the patient to a specialised centre for further analyses. Whether to start antibiotic treatment should be deliberated with experts in the field.

## Possible

### Possible chronic Q fever

- a. IFA IgG phase I titer  $\geq 1:1024$  without clinical manifestations described in category 1 'Proven chronic Q fever' and category 2 'Probable chronic Q fever'

Advice: refer the patient to a specialised centre for further analyses. Whether to start antibiotic treatment should be deliberated with experts in the field.