

Chronic Q fever

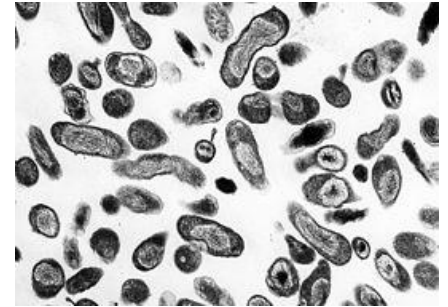
Chantal Bleeker-Rovers
Infectious Diseases specialist
Radboud Expertise Center for Q fever

Conflict of interest

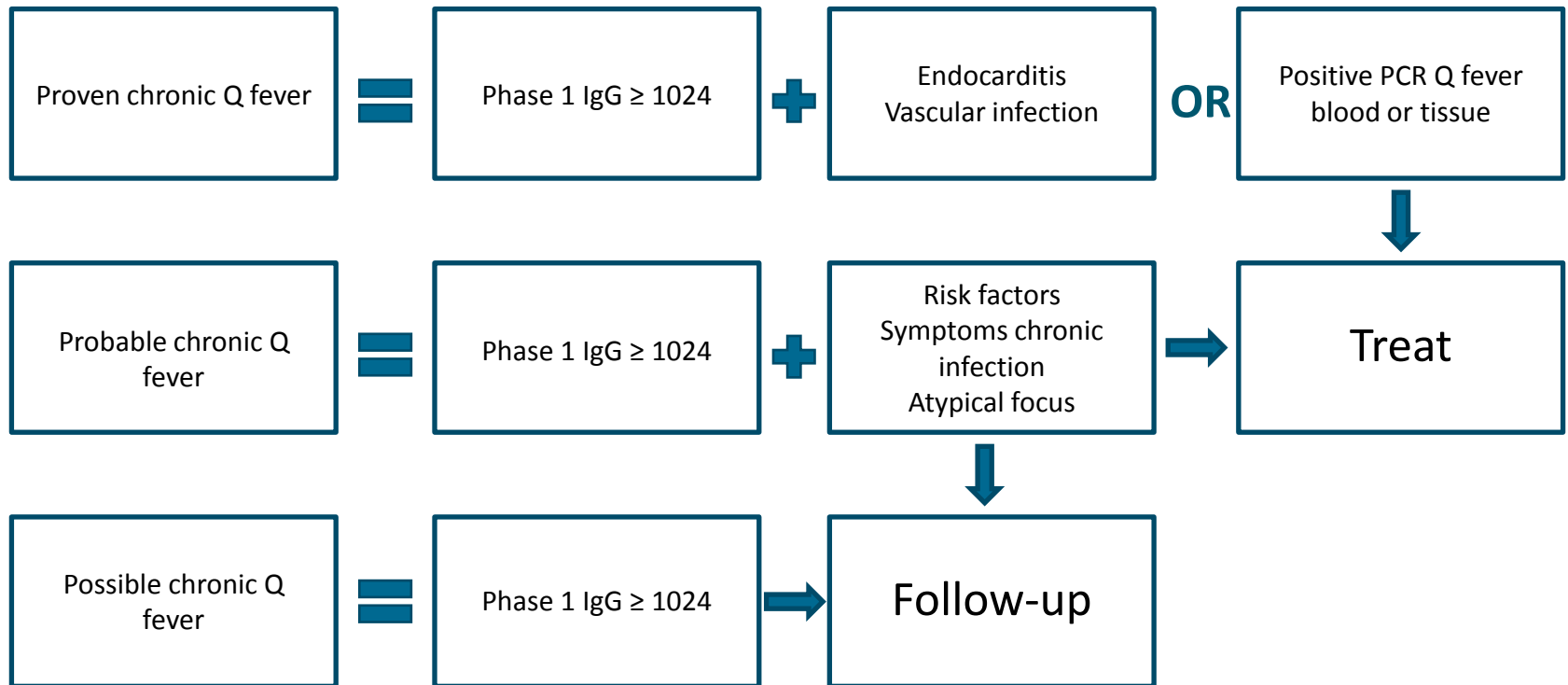
(potential) conflict of interest	None
Potentially relevant relationships with companies	None
<ul style="list-style-type: none">• Sponsorship or grant for research• Fee or other (financial) compensation• Shareholder• Other relationship	<ul style="list-style-type: none">• Research grants Q-support• None • None• None

Q fever outbreak the Netherlands

- Q fever:
 - zoonotic infection
 - *Coxiella burnetii*
- 2007 to 2010: Q fever outbreak the Netherlands:
 - >4000 patients notified with acute Q fever
 - >40,000 people infected
 - Localized in the southeastern part of the Netherlands
- Clinical syndromes:
 - Acute Q fever
 - Q fever fatigue syndrome
 - Chronic Q fever



Definition chronic Q fever



Q fever endocarditis

- 70-80% of all chronic Q fever patients
- The Netherlands: 35% of all chronic Q fever patients
- Usually in patients with underlying valve disease
- Vegetations often absent: difficult diagnosis!
- Revised Duke criteria: high anti-phase I antibody level
- Important cause of culture-negative endocarditis

Vascular chronic Q fever

- <10% of all chronic Q fever cases in France
- 60% of all chronic Q fever cases in the Netherlands
- Frequent complications:
 - Aneurysm rupture
 - Aorto-enteric fistulas with gastrointestinal bleeding
 - Paravascular abscesses
 - Spondyl(odisc)itis

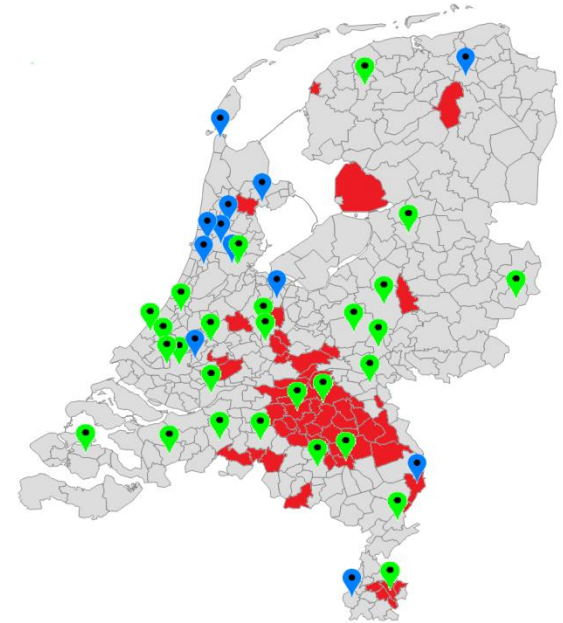
Dutch Chronic Q fever Database

UMC Utrecht

JEROEN BOSCH
ZIEKENHUIS

Radboudumc
university medical center

- Data of all known Dutch chronic Q fever patients
- Patients identified by:
 - Microbiology labs
 - Infectious diseases specialists
- Last complete update May 2016, planned in 2018
- 249 patients with proven chronic Q fever
 - 27% endocarditis
 - 50% vascular infection
 - 16% endocarditis and vascular infection
- 74 patients with probable chronic Q fever



Complications

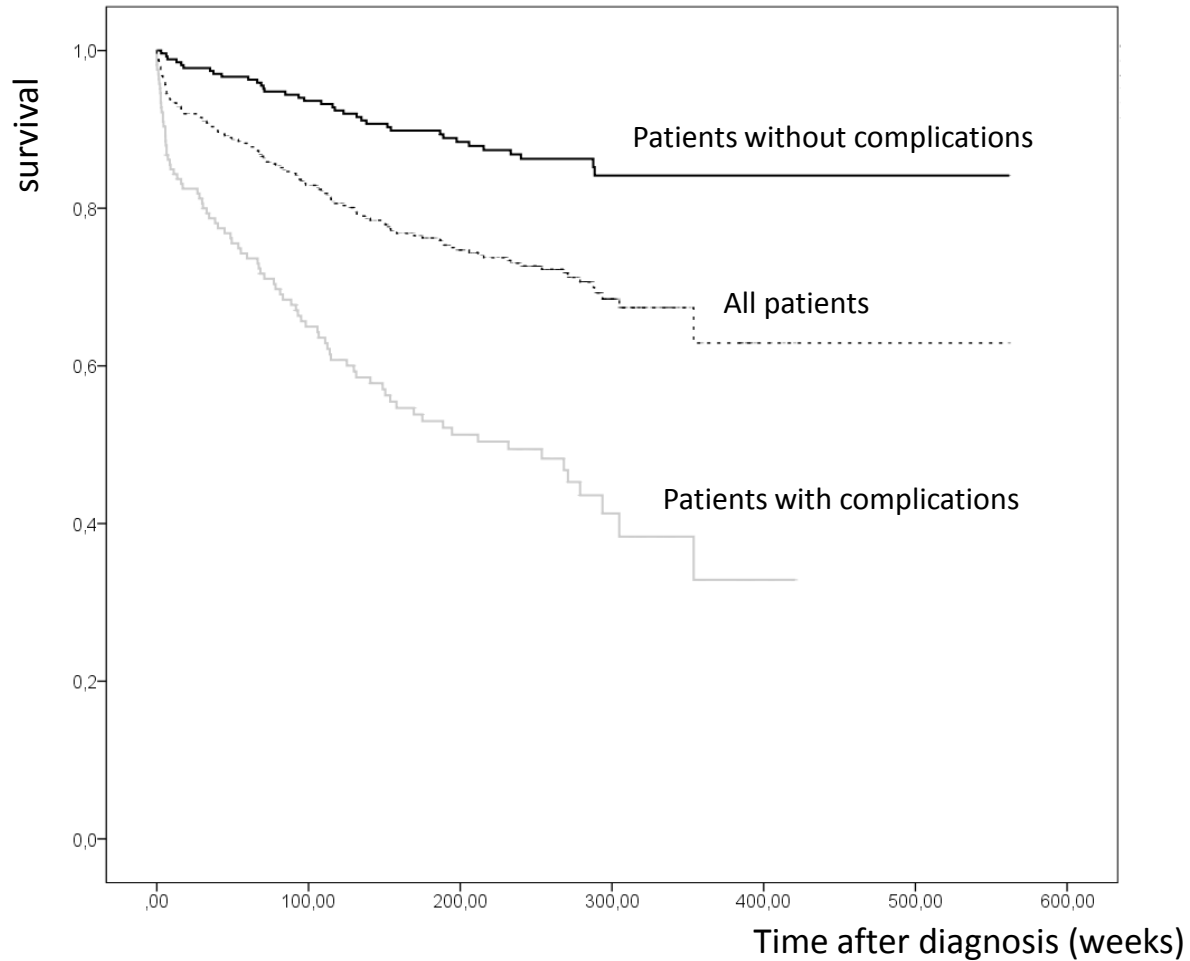
Update May 2016 database:

- 439 patients with chronic Q fever (until May 2012: 284 patients)
- Complications present:
 - 61% proven chronic Q fever
 - 15% probable chronic Q fever
 - 2% possible chronic Q fever
- 60% vascular chronic Q fever
- 48% Q fever endocarditis

Complications and mortality

	Complications (OR, 95% CI)	Mortality Q fever (OR, 95% CI)
Age	1.04 (1.02-1.06)	1.03 (1.00-1.06)
Prosthetic valve or vascular prosthesis	1.79 (1.07-2.99)	Ns
Positive serum PCR	2.25 (1.36-3.72)	Ns
Four-fold titer decrease	Ns	0.27 (0.12-0.58)
Complications	NA	8.20 (3.65-18.45)

Mortality chronic Q fever



Mortality chronic Q fever

- Proven chronic Q fever: 25%
- Probable chronic Q fever: 4%
- Possible chronic Q fever: none

- Endocarditis and vascular infection: 33%
- Vascular infection: 25%
- Endocarditis: 12%

Nog steeds nieuwe doden door Q-koorts

'Nooit gedacht dat er zoveel Q-koortsdoden zouden vallen'

DEN BOSCH - Als directeur van het centrum infectieziektenbestrijding van het RIVM had Roel Coutinho vanaf 2007 een belangrijke rol in de bestrijding van de Q-koortsuitbraak. Dat er [74 \(en waarschijnlijk meer\) mensen](#) aan de epidemie zouden overlijden had hij in 2007 nooit en te nimmer gedacht, zegt Coutinho, tegenwoordig hoogleraar Life Sciences aan de universiteit in Utrecht.



Screening for chronic Q fever

General population:

- 2014 (7 years after the start of the outbreak)
 - Screening Q fever serology 1517/2161 adult inhabitants of Herpen
 - Seroprevalence 33.8%
 - 2 known chronic Q fever patients
 - 1 new chronic Q fever patient
-
- 4.4% chronic Q fever in 69 patients with a known cardiovascular risk factor



Mysterieuze epidemie in Brabants dorp ^{23/6/07} *Gelderland*

Van de 3000 inwoners
melden zich 90 met
griepverschijnselen.

oorzaak van de ziektegevallen te
acherhalen. De uitslag is volgens
huisarts Rob Besselink waarschijn-
lijk volgende week al bekend.
Volgens de GGD Hart voor Bra-

Screening risk groups



Vascular infections:

- Jeroen Bosch Hospital and Bernhoven Hospital,
- November 2009 until January 2012
- Screening chronic Q fever (IFA) in all patients with:
 - AAA \geq 30 mm
 - Aneurysm iliac artery >12 mm
 - EVAR
 - Vascular prosthesis aorta or iliac arteries
- Seroprevalence Q fever among 770 patients: 16.9%
- Chronic Q fever in 30.8% of all patients with positive Q fever serology

Screening risk groups

Endocarditis:

- November 2010 until January 2011 in Jeroen Bosch Hospital
- Screening of all patients with previous heart valve surgery

- Seroprevalence among 568 patients: 20.4%
- Chronic Q fever in 7.8% of all patients with positive Q fever serology

Screening risk groups

Reumatoid arthritis:

- Area of Q fever outbreak, December 2011 until June 2012
- Screening of all patients with reumatoid arthritis

- Seroprevalence among 759 patients: 14.8%
- Chronic Q fever in 8.9% of all patients with positive Q fever serology

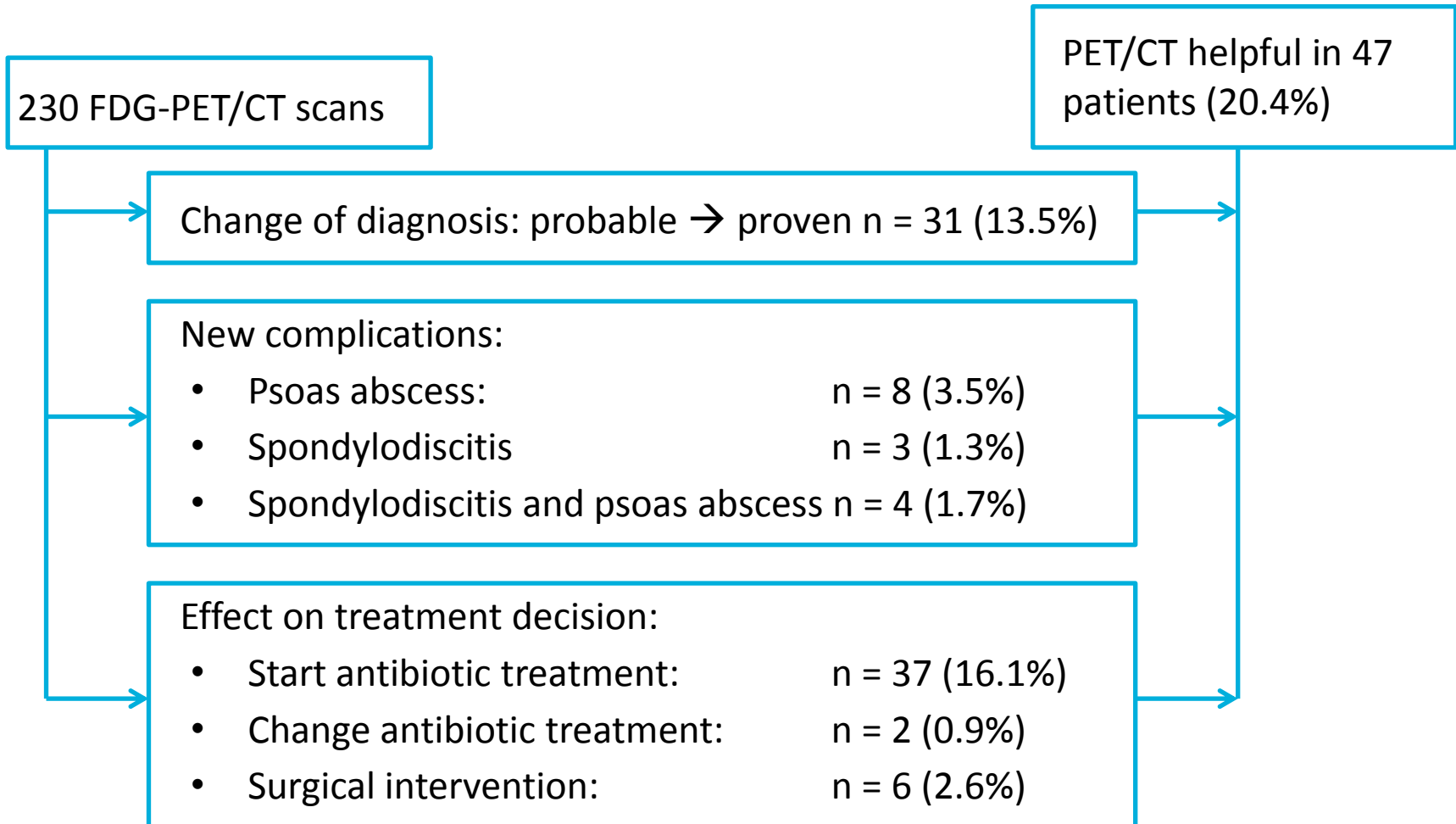
Dutch chronic Q fever database

- ~75% of all patients diagnosed with proven or probable chronic Q fever have a risk factor and can be identified by screening
- 68% of all patients has a complication before start of antibiotic therapy, so diagnosis came “too late”

FDG-PET/CT in chronic Q fever

- Localizing infection is difficult in chronic Q fever:
 - Vegetations often not seen on echocardiography
 - Chronic low-grade vascular infection easily missed on CT
- FDG-uptake in all activated inflammatory cells: sensitive imaging technique
- FDG-PET/CT has proven its diagnostic value in:
 - Diagnosing vascular infection
 - Prosthetic valve endocarditis (EASC guideline 2015)
- Low sensitivity of FDG-PET/CT for diagnosing native valve endocarditis (but high specificity)

FDG-PET/CT at diagnosis



FDG-PET/CT during follow-up

- 218 FDG-PET/CT scans performed in 143 patients
- Reason for follow-up scans:
 - Suspected new complications: n=175 (80.3%)
 - End of treatment evaluation: n=43 (19.7%)
- Change of diagnosis probable to proven chronic Q fever: n=2 (0.9%)
- Change of treatment: n=125 (57.3%)

FDG-PET/CT: patient

2012 abdominal aneurysm → EVAR

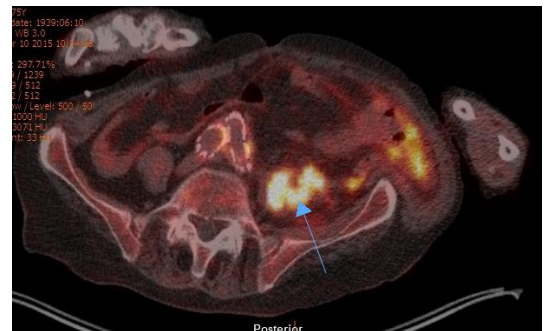
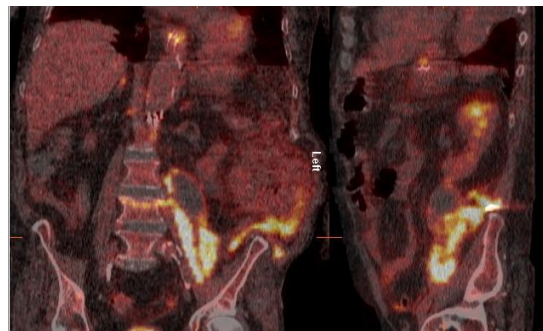
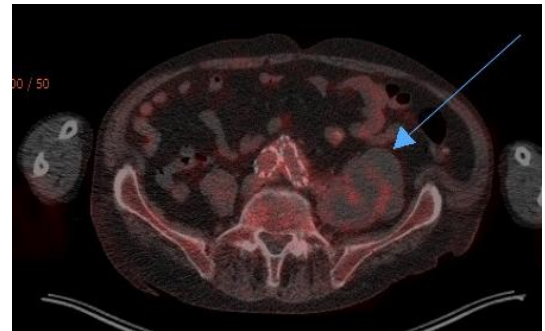
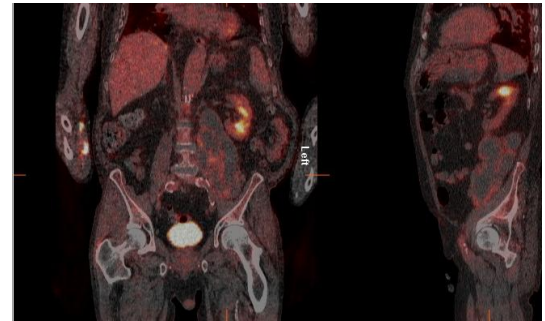
2015-01: malaise, weight loss 10kg, backache, no fever.

IFA phase I IgG antibodies: 1:4096.

FDG-PET/CT: minimally increased uptake around EVAR, psoas abscess.

Positive PCR psoas abscess.

2015-04: FDG-PET/CT:
FDG uptake around EVAR,
psoas, muscles, and
spondylodiscitis L4.



Treatment of chronic Q fever

- Tetracycline effective, but long-term treatment needed, many relapses
- Tetracyclines combined with quinolones more effective
- *C. burnetii* replicates within acidified phagolysosome in macrophages and monocytes decreasing bactericidal activity of antibiotics
- Alkalizing agent such as hydroxychloroquine increases pH in phagolysosome

Treatment of chronic Q fever

Table 3. Comparison of Outcomes Between the 2 Therapeutic Regimens

	Doxycycline and Ofloxacin (n = 14)	Doxycycline and Hydroxychloroquine (n = 21)	P*
Treatment duration among cured patients, mean ± SD, mo	56 ± 18	31 ± 14	<.001
Valve surgeries, No.	10	10	.16
Deaths, No.	1	1	.77
Relapses/completed treatments, No.	7/15	2/23	.01
Relapses after 18 mo of treatment, No.	6/11	0/16	.001
Decreasing slope of anti-phase I <i>Coxiella burnetii</i> antibodies			
IgG	-0.08	-0.10	r = 0.92 (NS)
IgM	-0.09	-0.09	r = 0.71 (Significant)
IgA	-0.08	-0.09	r = 0.76 (NS)
Photosensibilization, No.	14	21	NA
Irreversible cutaneous pigmentation, No.	1	1	.77

*NS indicates not significant; NA, not applicable.

- First-line treatment of chronic Q fever: doxycycline with hydroxychloroquine

Treatment of chronic Q fever

- Doxycycline with hydroxychloroquine many side effects:
 - Gastrointestinal
 - Phototoxicity (>90%)
 - Cutaneous hyperpigmentation
 - Retinopathy
- Treatment failure in some cases
- Need for alternative regimens



Treatment of chronic Q fever

- Descriptive retrospective observation cohort study with data from Dutch National Chronic Q fever Database
- Time-dependent Cox proportional hazards analysis to compare efficacy of different treatment regimens
- Reference regimen: doxycycline with hydroxychloroquine
- Comparator regimens:
 - Doxycycline with quinolone (with or without hydroxychloroquine)
 - Quinolone monotherapy
 - Doxycycline monotherapy

Treatment of chronic Q fever

- Outcome: overall mortality and therapy failure defined as:
 - New complication >6 weeks after initiation of treatment
 - New positive PCR having been negative >3 months
 - PCR-positivity persisting >6 months during treatment
 - Chronic Q fever related mortality

Treatment of chronic Q fever

- Outcome: overall mortality and therapy failure defined as:
 - New complication >6 weeks after initiation of treatment
 - New positive PCR having been negative >3 months
 - PCR-positivity persisting >6 months during treatment
 - Chronic Q fever related mortality
- 276 patients included:
 - 227 proven chronic Q fever (82%)
 - 49 probable chronic Q fever (18%)
- Mean treatment duration 2.0 years
- Doxycycline plus hydroxychloroquine used by 254 patients (92%)
- 160 patients (58%) used multiple regimens

Treatment of chronic Q fever

- Treatment with doxycycline plus quinolone or treatment with quinolone alone not associated with the primary outcome compared to tetracycline plus hydroxychloroquine

	DOX/HCQ	DOX/QLN	QLN
Number	254 (92%)	71 (26%)	93 (34%)
Overall mortality	27 (11%)	8 (11%)	13 (14%)
Chronic Q fever related mortality	22 (9%)	5 (7%)	10 (11%)
Complications	34 (13%)	11 (15%)	12 (13%)
Therapy failure	61 (24%)	12 (17%)	21 (23%)

- Treatment with quinolone or doxycycline monotherapy frequently discontinued due to subjective insufficient clinical response (29% and 59%)

Doxycycline levels

TABLE 1. Serum doxycycline concentration, MIC, and outcome for 16 patients with Q fever endocarditis^b

Patient no.	No. of dilution decrease	Serum doxycycline level (µg/ml) after 1 yr of treatment	Doxycycline MIC (µg/ml)	Serum/MIC ratio	Outcome	Duration of treatment (mo)
1	0	3.8 ± 0.4	4	1.0	Still under therapy	22
2	0	2.5 ± 0.1	4	0.6	Cured	44
3	1	3.9 ± 0.5	4	1.0	Dead ^a	19
4	1	2.2 ± 0.1	4	0.6	Cured	36
5	2	2.1 ± 0.2	4	0.5	Cured	60
6	2	2.7 ± 0.4	4	0.7	Still under therapy	24
7	3	4.0 ± 0.4	4	1.0	Cured	30
8	4	5.9 ± 0.6	2	3.0	Cured	35
9	4	3.9 ± 0.4	2	2.0	Cured	18
10	4	4.0 ± 1.4	2	2.0	Cured	29
11	4	3.2 ± 0.6	2	1.6	Cured	25
12	5	4.7 ± 0.8	2	2.4	Cured	36
13	5	8.3 ± 1.1	4	2.1	Dead ^a	19
14	10	2.9 ± 0.1	2	1.5	Cured	25
15	5	4.5 ± 0.7	1	4.5	Still under therapy	30
16	0	3.5 ± 0.6	8	0.4	Dead	14

^a These patients died without suffering an evolutive Q fever.

^b Patients 1 to 6 had decreases of IgG and/or IgA phase I antibody titers of ≤2 dilutions (group B). Patients 7 to 15 had decreases of IgG and/or IgA phase I antibody titers of ≥2 dilutions (group A). Patient 16 died during the course of treatment.

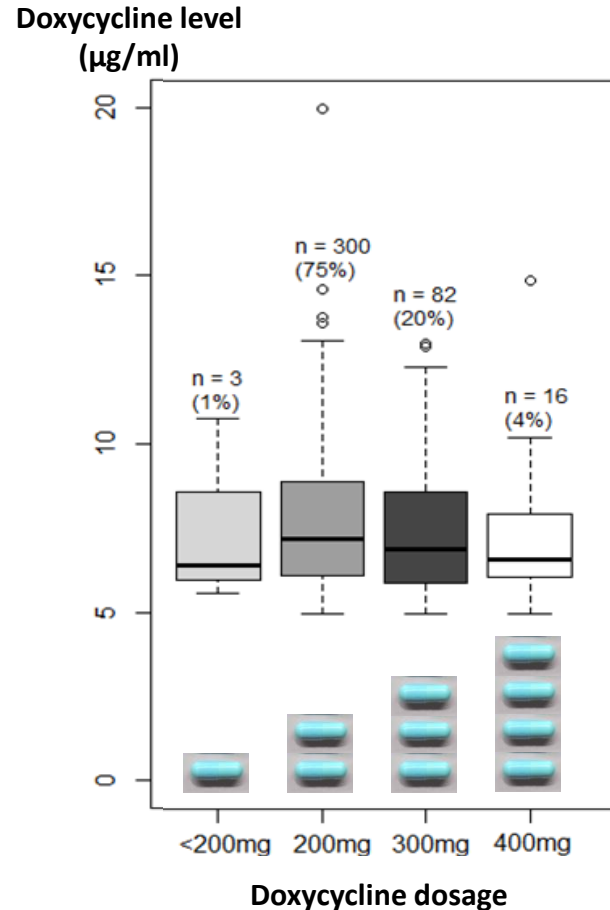
- High ratio serum doxycycline concentration/MIC (>1) associated with rapid decline in antibody levels

Doxycycline levels

- 201 patients with chronic Q fever treated with doxycycline >12 weeks:
 - In 167 patients (83%): treatment based on doxycycline concentrations
 - In 34 patients (17%): treatment not based on doxycycline concentrations
- Primary outcome: first disease-related event (new complication or Q fever related mortality) during or within one year after end of treatment
- Multivariable analysis with a Cox proportional hazards model adjusted for the intensity of patient care

Doxycycline levels

- Target level between 5 and 10 $\mu\text{g/ml}$
- In 145 patients (87%) serum concentration $>5 \mu\text{g/ml}$ reached

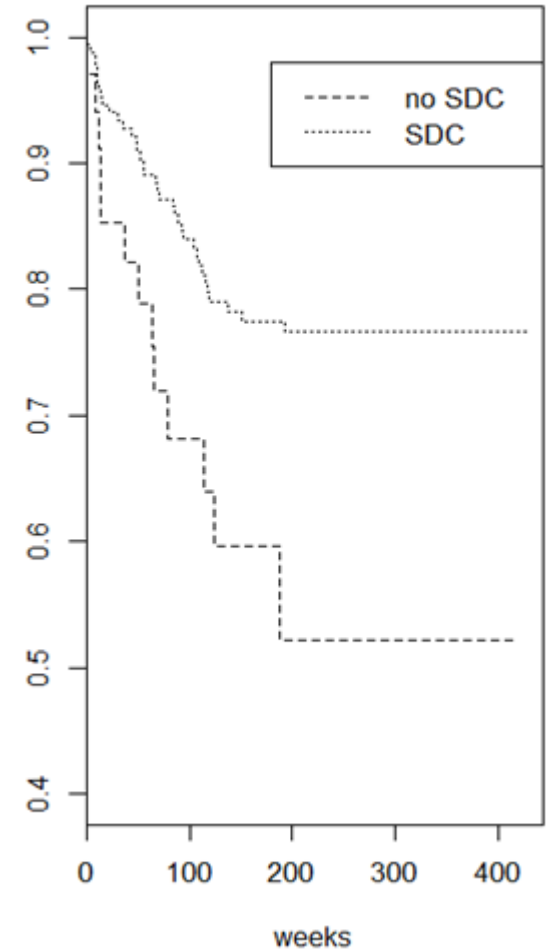


Doxycycline levels

- Disease-related events HR (95%CI): 0.50 (0.26-0.96)
- Advice for all patients treated with doxycycline for chronic Q fever:
 - measurement of serum doxycycline concentrations
 - titration of doxycycline dosage up to serum doxycycline concentrations $>5 \mu\text{g/ml}$



Disease-related events



Treatment chronic Q fever

- Treatment duration endocarditis at least 18 months
- Prosthetic heart valve at least 24 months
- Treatment duration in vascular infection unknown, in clinical practice (much) longer
- Treatment duration for other than preferred regimes longer (how long?)

Treatment can be stopped:

- Minimal treatment duration has been reached
- Four-fold titer decrease or phase I IgG ≤ 1024
- Serum PCR negative
- No active infection on imaging

Chronic Q fever: a complicated disease

- Think of chronic Q fever!
- Difficult diagnosis: FDG-PET/CT useful for diagnosis and during follow-up
- Difficult treatment:
 - Many side effects
 - Doxycycline with a quinolone appears to be a safe alternative to doxycycline with hydroxychloroquine
 - Determining doxycycline levels needed during doxycycline therapy

Thanks to:

- University Medical Center Utrecht, the Netherlands
 - Sonja van Roeden
 - Jan-Jelrik Oosterheert
- Jeroen Bosch Hospital:
 - Peter Wever
- Radboud university medical center and Radboud Expertise Center for Q fever, the Netherlands:
 - Ilse Kouijzer
- All hospitals, doctors, and patients participating in the Dutch Chronic Q fever Database



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