Netherland,
7 June 2012

« Public health authority versus knowledge: The Dutch Q fever outbreak paradigm »

Pr Didier RAOULT
didier.raoult@gmail.com
Marseille-FRANCE

EXPERT OPINION VS DUTCH CONSENSUS

A time expert definition lacking
(Rapport mission Bioterorisme D.Raoult. Chap 6 – L'expertise p.74)
http://www.timone.univmrs.fr/medecine/divers/MISSIONDR/RAPPORTMISSIONTOTALITE.pdf
and believing that true expert can be entirely replaced by student doing bibliography.

- Q fever definitions
- Acute Q fever
- "Chronic Q fever"

- Prevention strategies
- Clarifying definitions

EXPERT Vs CONSENSUS

Expert What is an expert?

Consensus - **E-CDC**
- **Dutch group**

Expert on acute Q fever

Dutch on acute Q fever - conclusion

Expert on Q fever and pregnancy

« consensus » on pregnancy - conclusion

Expert on « chronic Q fever »

- In general
- Endocarditis - Diagnosis
  - Treatment
  - Prevention
- Vascular infection
- Others

Dutch consensus on « chronic Q fever »

Conclusion

WHO IS AN EXPERT

- For many years very few investigators in the world work on Q fever that followed rickettsiologists.

Q FEVER. 1,838 RECORDS	
AUTHORS	**RECORD COUNT**
RAOULT, D	218
MEGE, JL	45
MARRIE, TJ	42
CAPO, C	34
HIRAI, K	32
RODOLAKIS, A	32
LEPIDI, H	30
SAMUEL, JE	28
FUKUSHI, H	27
HEINZEN, RA	27
WILLIAMS, JC	27
KOVACOVA, E	23
YAMAGUCHI, T	23
TISSOT-DUPONT, H	22
KAZAR, J	22
BROUQUI, P	20
MARMION, BP	20
ROLAIN, JM	19
STEIN, A	19
TOMAN, R	19

8/20 in Marseille

Dutch Q fever Consensus Group.Collaborators (27)
Bijlmer HA, Bleeker-Rovers C, Delsing CE, Galama JM, Herremans T, Hogema BM, Horrevorts AM, Kampschreur LM, van Kasteren M, Koopmans MP, Lestrade P, van Loo IH, Marcelis J, Nabuurs-Franssen MH, Notermans DW, Oosterheert JJ, Renders NH, Schneeberger PM, Sprong T, van Steenbergen J, Teijink JA, Vlaminckx BJ, van der Voort PH, de Vries JP, Wegdam-Blans MC, Wever PC, Zaaijer HL.

Chronic Q fever: review of the literature and a proposal of new diagnostic criteria.
Wegdam-Blans MC, Kampschreur LM, Delsing CE, Bleeker-Rovers CP, Sprong T, van Kasteren ME, Notermans DW, Renders NH, Bijlmer HA, Lestrade PJ, Koopmans MP, Nabuurs-Franssen MH, Oosterheert JJ; Dutch Q fever Consensus Group.
J Infect. 2012 Mar;64(3):247-59. Epub 2011 Dec 23.

- May data come from a single place (mine).

Rapport mission Bioterorisme D.Raoult. Chap 6 – L'expertise p.74

http://www.timone.univ-mrs.fr/medecine/divers/MISSIONDR/RAPPORTMISSIONTOTALITE.pdf

Expertise

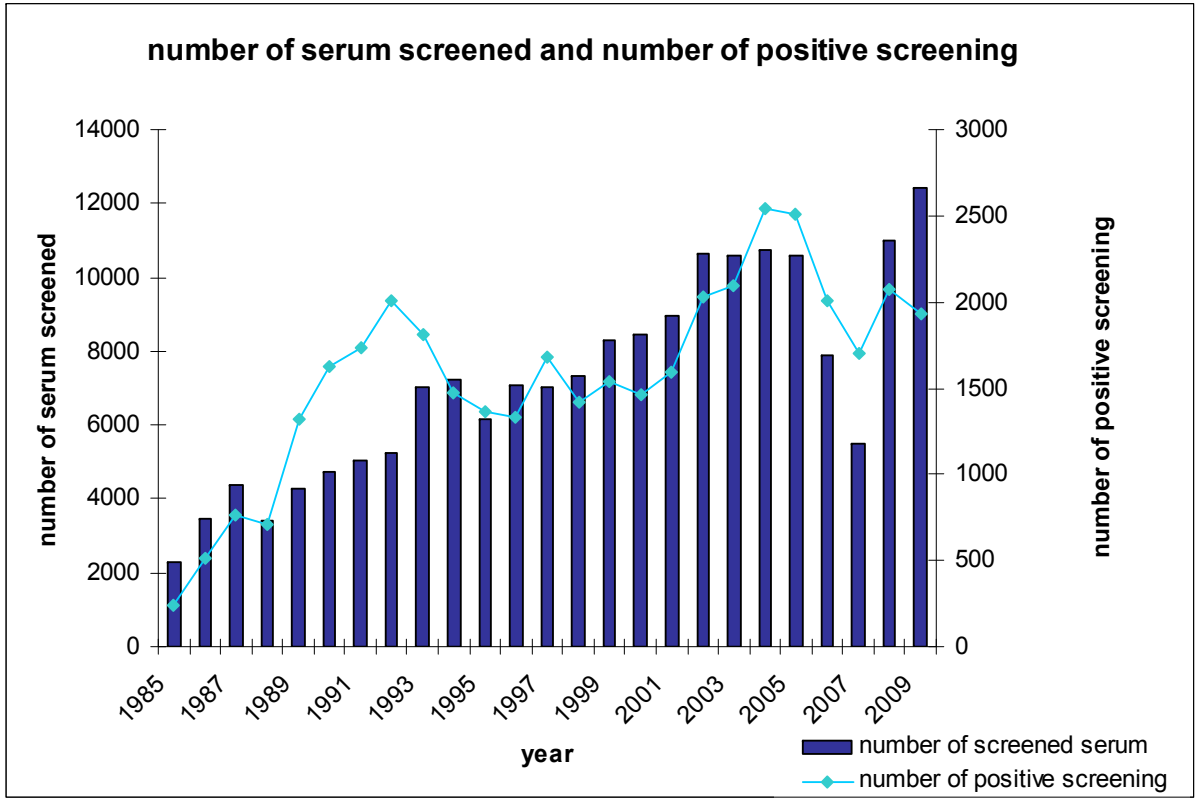
Established an initial description describing the expert's profile in order to selecting him or with the required skills. Systematically check their competencies (with CVs matching the required and using PubMed as a resource).

Marseille

25 years of monitoring of the Q fever at the CNR of Rickettsies

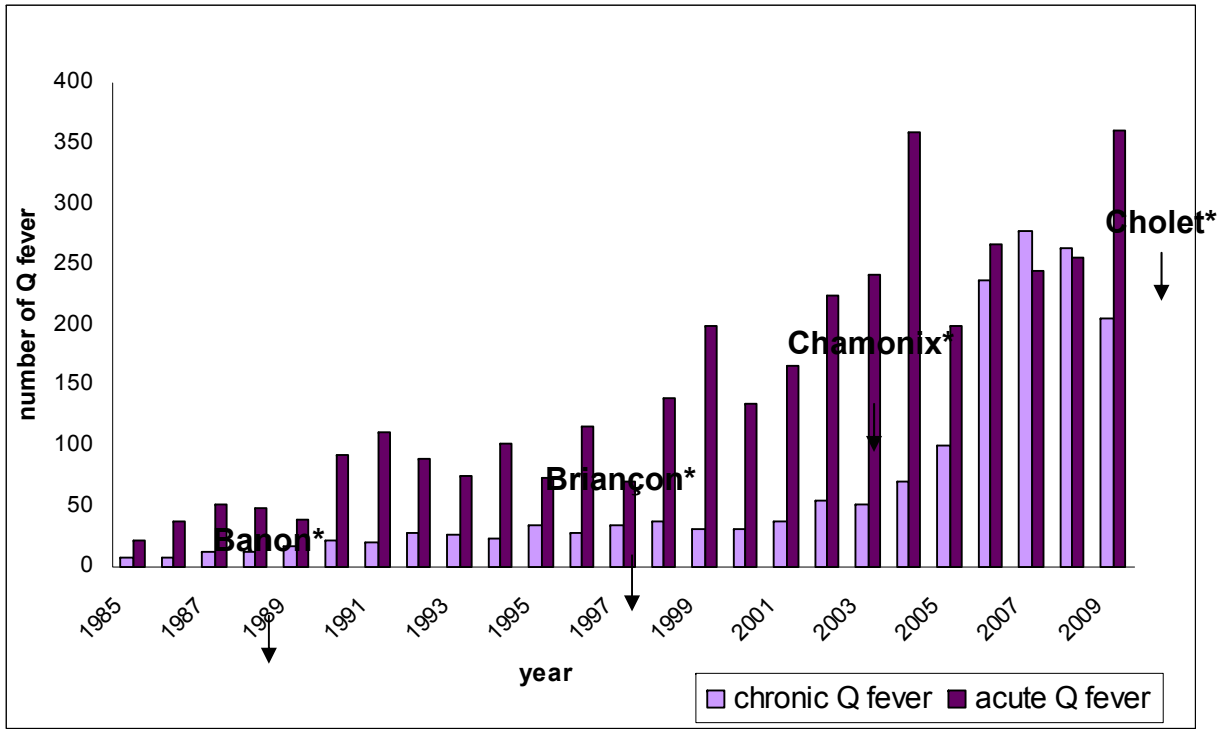
WHO reference center since 1988 for Rickettsioses

Ask Q fever



- 179.794 analyzed serums, 39.472 positive at screening dilution (30%)
- Increase in demand each year (except in 2006 and 2007)
- Increase in positive test (two peaks: 1992 and 2004)

Epidemics described by CNR (1)



Among these that we investigated in France we find the source in all cases.

When health autorities investigated = no source found

Fig 2. Acute and Chronic Q fever from 1985 to 2009. * places where outbreaks were reported.

Epidemics in Europe from 1987 to 2009

Year Pub	outbreak	n° of cases	ref
Scotland:			
2006	2006	51	25
2008	2006	138	26
UK :			
2004	2002	95	27
2010	2007	30	28

Netherland :

Year Pub	outbreak	n° of cases	ref
2010	2007	168	29
	2008	1000	
	2009	2357	
2010	2008	28	30

Germany:

Year Pub	outbreak	n° of cases	ref
1997	1996	45	b [23]
1996	1994	18	c [23]
2006	2003	299	31
2007	2005	331	32

France :

Year Pub	outbreak	n° of case	ref
1992	1987	40	f [23]
1999	1990-1995	289	m [24]
2002	1996	29	d [23]
1999	1996	5	h [23]
2003	2000	10	j [24]
2003	2000	5	k [24]
2004	2000	17	41
2006	2002	101	14
unpub	2009	50	unp

Year Pub	outbreak	n° of cases	ref
Poland:			
1996	1992-94	25	e [23]
Slovakia :			
1998	1993	113	g [23]
Slovenia:			
2007	2007	36	33
Croatia:			
2005	2004	14	34
Bosnia			
2003	1997	26	l [24]
Kosovo:			
2007		59	35
Bulgaria:			
2009	2004	220	36

Spain :

Year Pub	outbreak	n° of cases	ref
2007	2003	60	39
2006	2004	22	40

Italy :

Year Pub	outbreak	n° of cases	ref
1999	87-88	235	n [24]
1996	93	58	a [23]
2004	2003	133	i [24]
2005		65	33

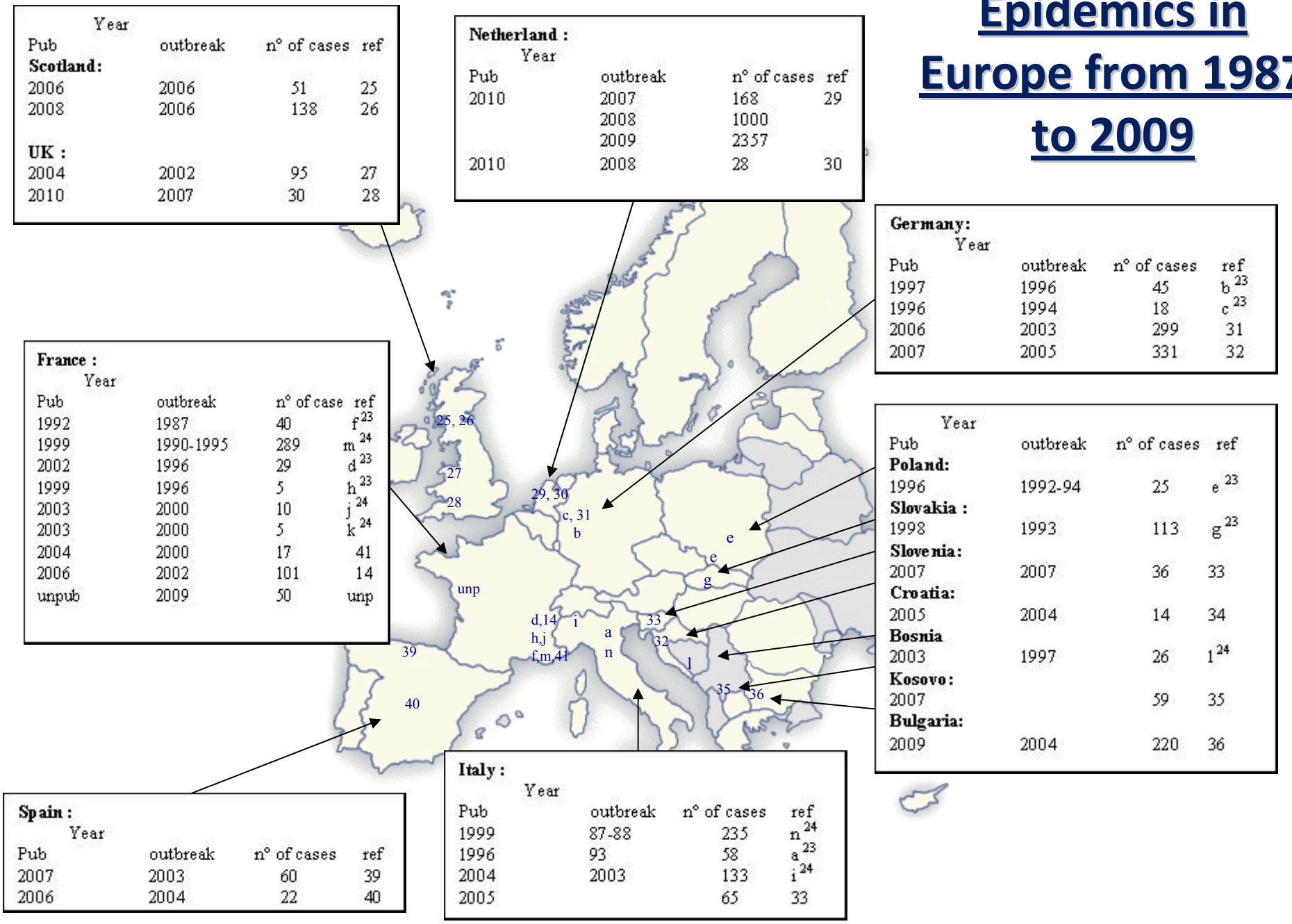


Fig 8. European outbreaks from 1987 to 2009

Expert opinion versus literature analysis and consensus The chronic Q fever paradigm. Raoult D.J Infect. 2012 Apr 23.

In 2011		
Microbiology		
- Serology		
- tested sera	**14,648**	
- quantification (IgGI MA phase I and II)		1,769
- Molecular testing by PCR	**4593**	
- blood		2057
- valves		247
- others		2289
- Culture (positive / attempt)		15/92
Medical information and follow up		
- Files generated by positive tests*	**894**	
- Acute infections		345
- Endocarditis		434
- Vascular infection		84
- Pregnancy		31
- Consultation (DR)	**208**	
- Information by phone		182
- Information by Email		473
- (including after testing)		115

* This include follow up and there are more file than patients.

New cases	**209**	
- Acute Q Fever		198
- with valvulopathy		13
- with other risk factors		14
- Endocarditis		28
- Vascular infection		9
- Pregnancy		3
- Others		25

Peoples working in the center	**8**	
- Doctors (MD, PhD)		4
- Technicians		3
- Administrative		1

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Dutch on acute Q fever - conclusion

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Expert on « chronic Q fever »

- In general
- Endocarditis
  - Diagnosis
  - Treatment
  - Prevention
- Vascular infection
- Others

Dutch consensus on « chronic Q fever »

Conclusion

Applicability of evidence-based practice in public health: risk assessment on Q fever under an ongoing outbreak. Forland F, De Carvalho Gomes H, Nokleby H, Escriva A, Coulombier D, Giesecke J, Jansen A. Euro Surveill. 2012 Jan 19;17(3):20060.

Query fever: an opportunity to understand the disease better. Coulombier D. Euro Surveill. 2010 Mar 25;15(12).

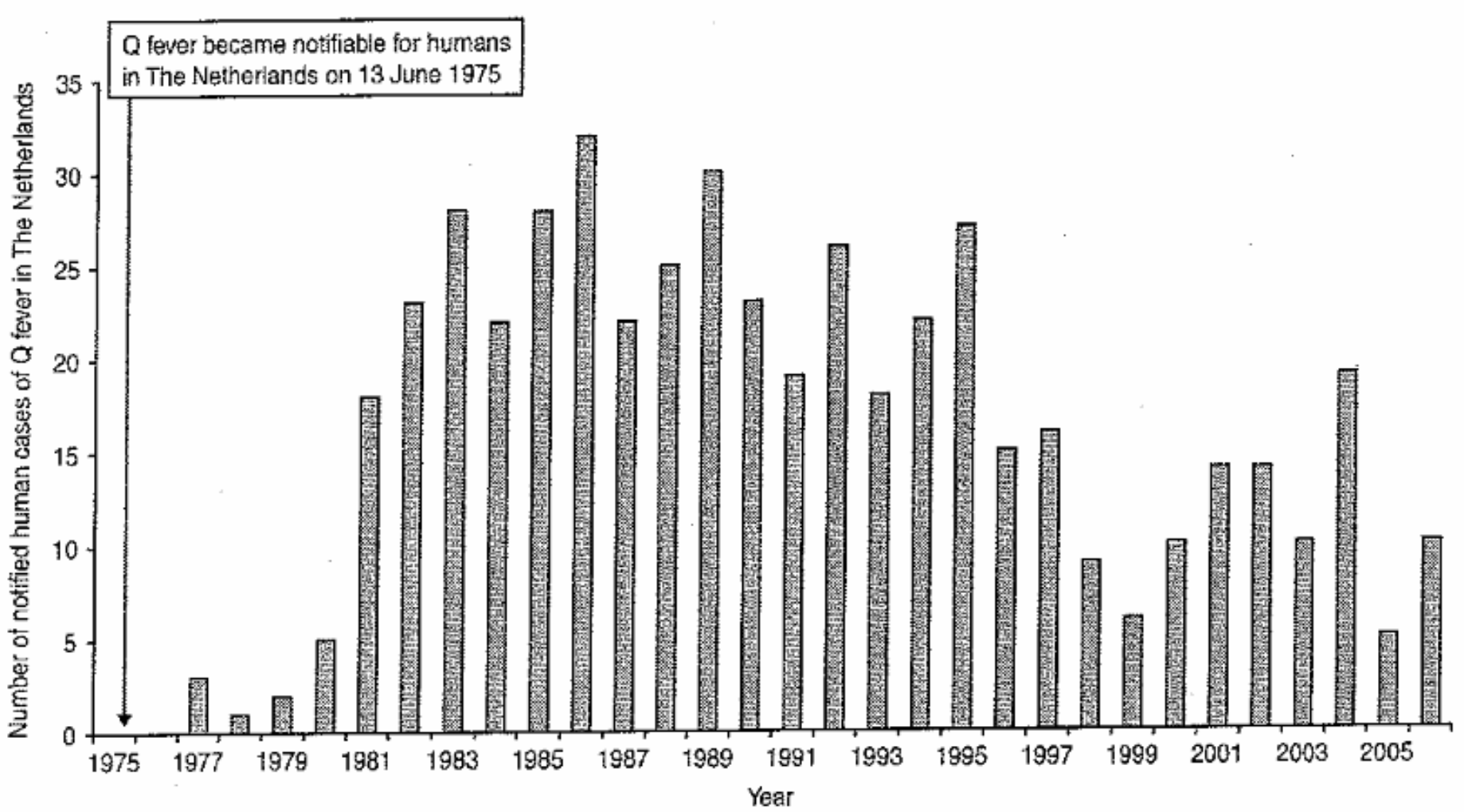
Late relapse of Q fever endocarditis. Morguet AJ, Jansen A, Raoult D, Schneider T. Clin Res Cardiol. 2007 Jul;96(7):519-21.

The Q fever epidemic in The Netherlands: history, onset, response and reflection

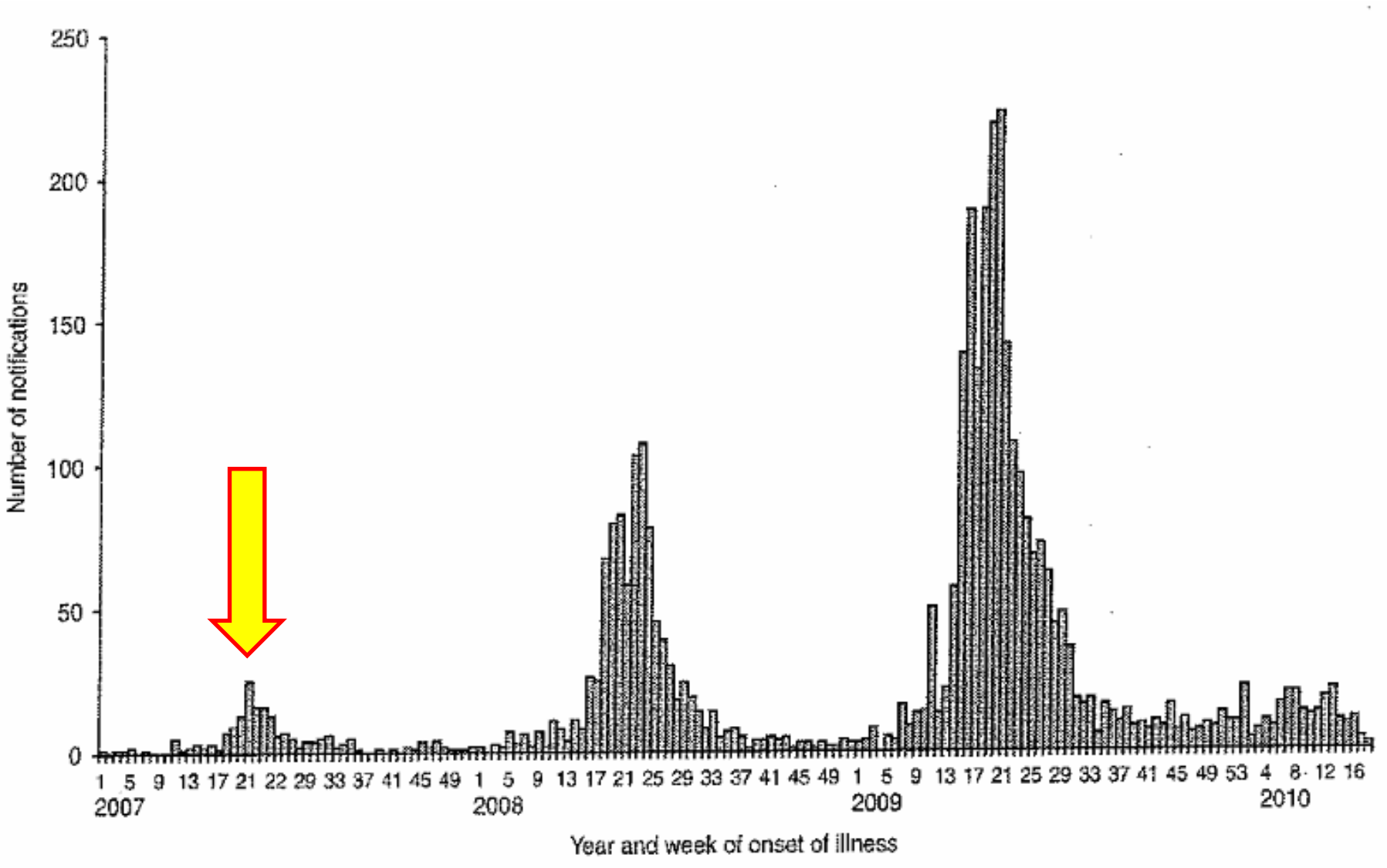
Roest HI, Tilburg JJ, van der Hoek W, Vellema P, van Zijderveld FG, Klaassen CH, Raoult D.

Epidemiol Infect. 2011 Jan;139(1):1-12.

Number of notified human cases in The Netherlands between 1975 and 2006



Number of notified human Q fever cases with a known first day of illness according to the week of onset of symptoms, from 1 January 2007 to 11 May 2010



Tender Specifications
for
Epidemiologic situation analysis of Tick Borne Encephalitis and Rickettsiosis in the European Union
Service Contract
Publication Reference: OJ/2010/01/08-PROC/2010/001
January 2010

http://www.ecdc.europa.eu/en/aboutus/calls/Lists/Calls%20for%20tender/ECDC_DispForm.aspx?List=a70e951a%2D9260%2D4909%2Dbc27%2Dcefd2af6e9a4&ID=503&RootFolder=%2Fen%2Faboutus%2Fcalls%2FLists%2FCalls%20for%20tender

We candidated and failed Poland: No *Rickettsia*, no *Coxiella*!

European Centre for Disease Prevention and Control

RICKETTSIOSES AND TICK BORNE DISEASES
Tender Specifications for Epidemiologic situation analysis of Tick Borne Encephalitis and Rickettsiosis in the European Union. Service Contract Publication Reference: OJ/2010/01/08-PROC/2010/001 January 2010

INFORMATION ON TICK-BORNE ENCEPHALITIS (TBE):

Denmark
SSI: Centraleuropæisk hjernebetændelse

Finland
Terveyden Ja Hyvinvoinnin Laitos: Puutiaisaivotulehdus

Germany:
Robert Koch Institut: FSME Risikogebiete in Deutschland

Norge
Folkehelseinstituttet: Skogflått

Poland
Polskiego Towarzystwa Wakcynologii: Szczepionka przeciwko kleszczowemu zapaleniu mózgu

Sweden:
SMI: Sjukdomsinformation om TBE

Czech Republic
Státní zdravotní ústav: Klíšťová encefalitida

UK:
NHS: Tick-borne encephalitis

We (Fournier PE, et al.TECHNICAL PROPOSAL : T-BRICK.ECDC public tender OJ/2010/01/08 – PROC/2010/001: "Epidemiologic situation analysis of Tick Borne Encephalitis and Rickettsiosis in the European Union") were candidate and failed versus people without scientific production

TECHNICAL REPORT
Risk assessment on Q fever

Expert panel
A meeting with experts from Europe and the USA was held in Paris on 9 April 2010.

Why Paris?

Surname	First name	Institute	Country	Total publication	Q fever publications
Asher	David	United States Food and Drug Administration	USA	13	0
Bernard	Helen	Robert Koch Institute	Germany	11	0
Coutino	Roel	RIVM (National Institute for Public Health and the Environment)	Netherlands	3	0
Daurat	Gerald	Agence Régionale de Santé	France	9	1
De Valk	Henriette	Institut de Veille Sanitaire	France	23	1
Desenclos	Jean-Claude	Institut de Veille Sanitaire	France	58	1
Holmberg	Jerry	United States Department of Health and Human Services	USA	157	0
Kirkbride	Hilary	Health Protection Agency	UK	8	0
More	Simon	University College Dublin	Ireland	41	0
Scheenberger	Peter	Jeroen Bosch hospital	Netherlands	28	0
van der Hoek	Wim	RIVM (National Institute for Public Health and the Environment)	Netherlands	101	10 + 1
van der Poel	Cees	Sanquin blood transfusion organization	Netherlands	115	0
van Steenbergen	Jim	RIVM (National Institute for Public Health and the Environment)	Netherlands	36	2
Villanueva	Silvia	Directorate-General for Health and Consumers, European Commission	Luxembourg	96	0
Coulombier	Denis	ECDC		55	1
Forland	Frode	ECDC		12	1
Giesecke	Johan	ECDC		159	1
Jansen	Andreas	ECDC		72	2
Nilsson	Monica	ECDC		15	0
Guichard	Catherine	Ministry of Health	France	84	0
Mailles	Alexandra	Institut de Veille Sanitaire	France	32	0
Pouchol	Elodie	French Health Products Agency	France	3	0
Rousset	Elodie	French Food Agency	France	23	0; 7

ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

No expert in Metaanalysis or Q fever

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Expert on « chronic Q fever »

- In general
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Dutch consensus on « chronic Q fever »

Conclusion

EXPERT OPINION ON ACUTE Q FEVER DEFINITION

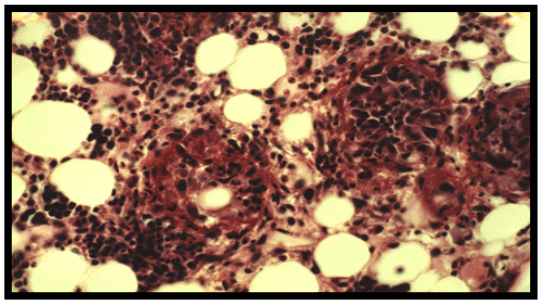
Recent fever/ transaminasitis/ pneumonia

and

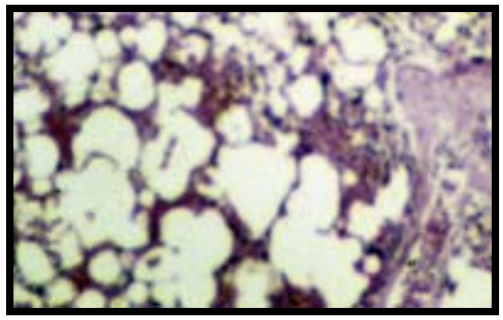
Presence of IgM and IgG against *C.burnetii*

ACUTE Q FEVER :

Variations from country to country



Hepatitis or pneumonia ?



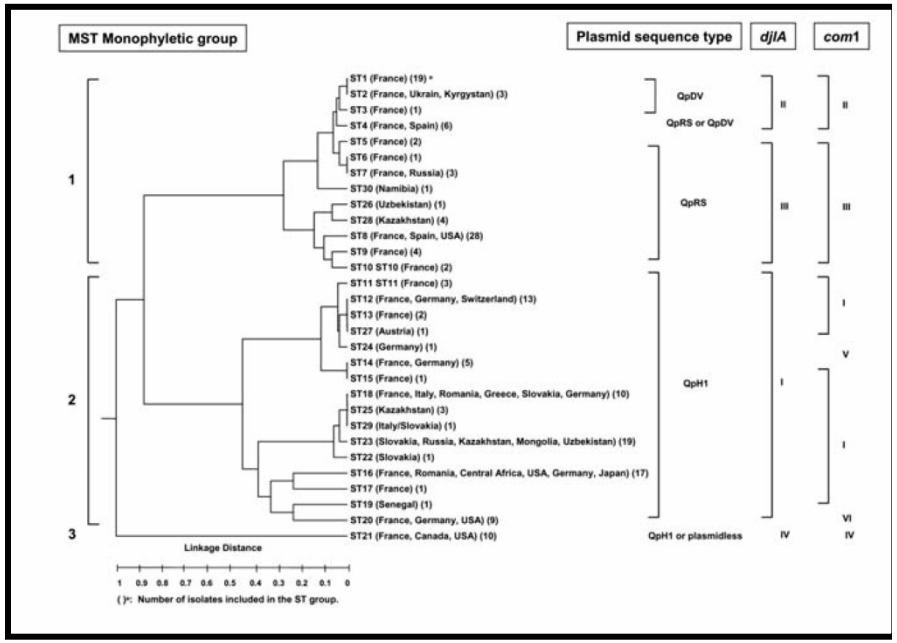
	Hepatitis	Pneumonia	Febrile illness
Basque county	+	+++	+
Andalusia	+++	+	++
France	+++	+	+
Canada	+	+++	+
Australia	+++	+	+

Maurin M, Raoult D. Q fever. Clin Microbiol Rev. 1999 ;12:518-53.

ROLE OF STRAINS IN ACUTE Q FEVER

- **Acute infection :**
  - Nine Mile lower inoculum for lung lesion than Priscilla

Stein A, et al. Q fever pneumonia: virulence of Coxiella burnetii pathovars in a murine model of aerosol infection. Infect Immun. 2005;73:2469-77.



  - Priscilla group: no isolate from acute infection

Glazunova, et al. Coxiella burnetii genotyping. Emerg Infect Dis. 2005;11:1211-7.

➢ Conclusion acute Q fever diagnosis is based on clinical finding and increase/ IgM using proper serology

➢ PCR remain to be evaluated! Including positive cases and negative controls

DUTCH DEFINITION OF ACUTE Q FEVER

- Pharynged swab positive for C.burnetii using PCR
- No validation, carriage? False positive?
- in our experience tested 1/50 confirmed Q fever

In the lab 1/602

Validity to be confirmed!

Clinical findings in Netherland identical

Types of tests realised by the POC in 2011

TESTS	Nb	%
Flu	5378	18
RSU	3844	12.9
Streptococcus A	3193	10.7
Legionella urine	2694	9
Pneumococcus urine	2642	8.8
PCR M.pneumoniae	2039	6.8
Rotavirus	1534	5.1
Adenovirus	1516	5.1
Streptotococcus B	845	2.8
Clostridium.difficile	668	2.2
PCR N.meningitidis	650	2.2
PCR Enterovirus	624	2.1
HIV rapid test	607	2
PCR Coxiella burnetii	605	0
Procaloitonine	456	1.5
PCR Herpes virus	363	1.2
Varicelle zona virus		

TESTS	Nb	%
PCR S.pneumoniae	359	1.2
Malaria	358	1.2
CSF	345	1.2
PCR Bordetella.pertussis	322	1.1
Cell count cryptococcus	246	0.8
EBV	177	0.6
Dengue	133	0.4
PCR Staphylococcus aureus	89	0.3
Helicobacter pylori	72	0.2
Norovirus	54	0.2
PCR Atopobium.vaginae	22	0.1
PCR Pneumocystis jiroveci	19	0.1
Tetanos	18	0.1
TOTAL	29872	100
ALL < 2 ½ h		

We used PCR based on 1111 Is since 2001

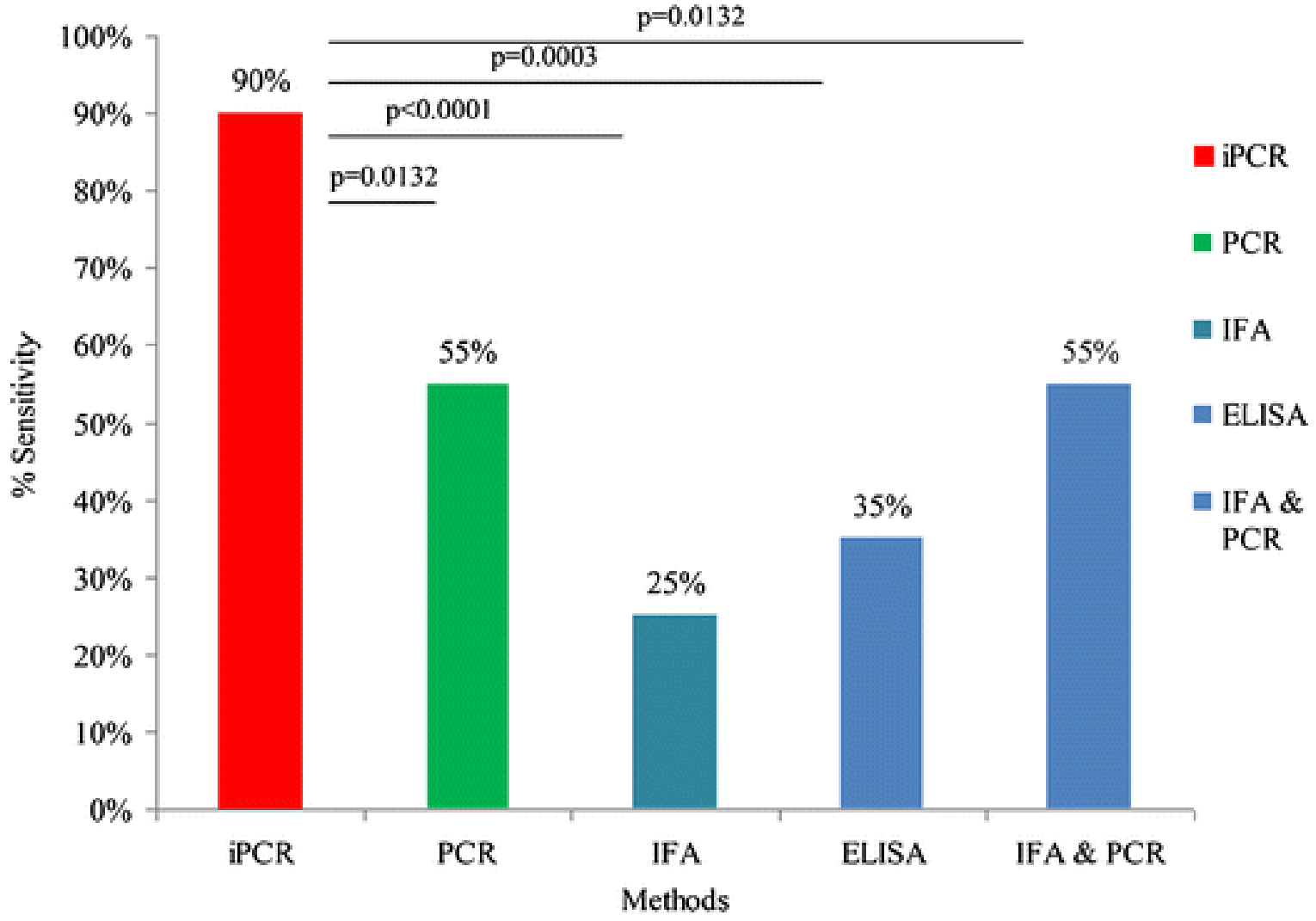
Comparison of PCR and serology assays for early diagnosis of acute Q fever.
Fournier PE, Raoult D.
J Clin Microbiol. 2003 Nov;41(11):5094-8

and q PCR since 2004

Molecular detection of Coxiella burnetii in blood and sera during Q fever.
Rolain JM, Raoult D.
QJM. 2005 Aug;98(8):615-7; author reply 617-20.

Immuno-PCR for the early serological diagnosis of acute infectious diseases: the Q fever paradigm.

Malou N, Renvoise A, Nappez C, Raoult D. Eur J Clin Microbiol Infect Dis. 2012 Jan 10.



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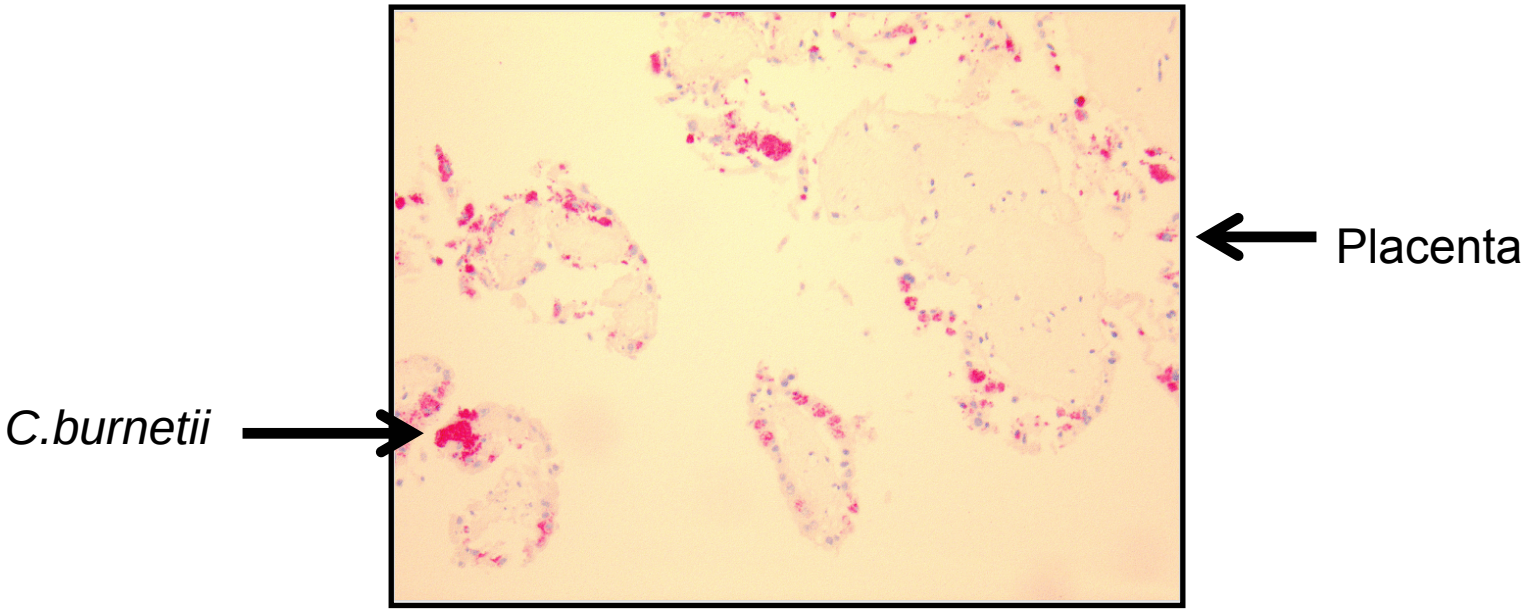
Q FEVER AND PREGNANCY

Expert opinion there are cases of abortions with death of the fetus, culture positive, immunohistochemistry positive



Human placenta

Coxiella burnetii seropositivity in parturient women is associated with adverse pregnancy outcomes.
Langley JM, Marrie TJ, Leblanc JC, Almudevar A, Resch L, Raoult D. Am J Obstet Gynecol. 2003 Jul;189(1):228-32.

CONCLUSION: About 4% (291/7658) of parturient women in this endemic area have evidence of previous exposure to *C burnetii and this exposure is associated with adverse pregnancy outcomes. The pathogenesis of this association* remains to be determined.

Q FEVER DURING PREGNANCY: DIAGNOSIS, TREATMENT, AND FOLLOW-UP

Raoult D, Fenollar F, Stein A.

Arch Intern Med. 2002 Mar 25;162(6):701-4.

BACKGROUND: Q fever, caused by Coxiella burnetii, may result in abortions, premature deliveries, and stillbirths in infected pregnant women.
OBJECTIVE: To evaluate the best treatment strategy for Q fever during pregnancy.
METHODS:
We evaluated the prognosis of 17 pregnant women who developed Q fever with and without co-trimoxazole (trimethoprim-sulfamethoxazole) treatment.
RESULTS: The outcome of the pregnancy was found to depend on the trimester. Abortions occurred in 7 of 7 insufficiently treated patients infected during the first trimester vs 1 of 5 patients infected later. Co-trimoxazole given until delivery protected against abortion (0/4) but not against the development of chronic infections, and it did not significantly reduce the colonization of the placenta (2/4 vs 4/4).
CONCLUSIONS: Our results show that C burnetii infections cause abortion and that women who develop Q fever while pregnant should be treated with co-trimoxazole for the duration of pregnancy, specifically when infected during the first trimester.

Managing Q fever during pregnancy: the benefits of long-term cotrimoxazole therapy

Carcopino X, Raoult D, Bretelle F, Boubli L, Stein A.

Clin Infect Dis. 2007 Sep 1;45(5):548-55.

Abstract

BACKGROUND:

Q fever is a zoonosis caused by Coxiella burnetii. During pregnancy, it may result in obstetric complications, such as spontaneous abortion, intrauterine growth retardation, intrauterine fetal death, and premature delivery. Pregnant women are exposed to the risk of chronic Q fever.

METHODS:

We included 53 pregnant women who received a diagnosis of Q fever. We compared the incidence of obstetric and maternal Q fever complications for women who received long-term cotrimoxazole treatment (n=16) with that for women who did not receive long-term cotrimoxazole treatment (n=37); long-term cotrimoxazole treatment was defined as oral administration of trimethoprim-sulfamethoxazole during at least 5 weeks of pregnancy.

RESULTS:

Obstetric complications were observed in 81.1% of pregnant women who did not receive long-term cotrimoxazole therapy: 5 (13.5%) women experienced spontaneous abortions, 10 (27%) experienced intrauterine growth retardation, 10 (27%) experienced intrauterine fetal death, and 10 (27%) experienced premature delivery. Oligoamnios was observed in 4 patients (10.8%). Obstetric complications were found to occur significantly more often in patients infected during their first trimester of pregnancy than in those infected later (P=.032). The outcome of the pregnancy was found to depend on placental infection by C. burnetii (P=.013). Long-term cotrimoxazole treatment protected against maternal chronic Q fever (P=.001), placental infection (P=.038), and obstetric complications (P=.009), especially intrauterine fetal death (P=.018), which was found to be related to placental infection (P=.008).

CONCLUSIONS:

Q fever during pregnancy results in severe obstetric complications, including oligoamnios. Because of its ability to protect against placental infection, intrauterine fetal death, and maternal chronic Q fever, long-term cotrimoxazole treatment should be used to treat pregnant women with Q fever.

Q fever and pregnancy

Mouse models

- Mice with repeated pregnancies over a 2 years period infected with *C. burnetii* Nine Mile strain:
  - Disseminated infection
  - Mortality <10 %
  - Endocarditis in 20 % of the animals
  - Associated to abortions and stillbirths

Stein A. *et al.* Repeated pregnancies in BALB/c mice infected with *Coxiella burnetii* cause disseminated infection, resulting in stillbirth and endocarditis. *J Infect Dis. 2000;181:188-94.*

Placental histopathology after Coxiella burnetii infection during pregnancy

Munster JM, Leenders AC, Hamilton CJ, Hak E, Aarnoudse JG, Timmer A.

Placenta. 2012 Feb;33(2):128-31

Abstract: Symptomatic and asymptomatic *Coxiella burnetii* infection during pregnancy have been associated with obstetric complications. We described placental histopathology and clinical outcome of five cases with asymptomatic *C. burnetii* infection during pregnancy and compared these cases with four symptomatic cases from the literature. In contrast with the symptomatic cases, we did not observe necrosis or active inflammation in the placentas of the asymptomatic women. Obstetrical outcome was more favourable in the asymptomatic cases than in the symptomatic cases. Asymptomatic and symptomatic *C. burnetii* infection during pregnancy are different entities with respect to placental histopathology and the risk of obstetric complications.

REPONSE LETTER

Matthieu MILLION[1], Hubert LEPIDI[1], Didier RAOULT[1], Andreas STEIN[1,2*]

[1]URMITE -CNRS UMR 6236 IRD 198, IFR 48, Faculté de Médecine, Université de la Méditerranée, Marseille, France

[2]Service de maladies infectieuses, Hôpital de la Conception, Marseille, France *Corresponding author

Screening for Coxiella burnetii infection during pregnancy: pros and cons according to the Wilson and Jungner criteria. Munster JM, Steggerda LM, Leenders AC, Aarnoudse JG, Hak E.Euro Surveill. 2012 Jan 19;17(3):20061.

Q fever and spontaneous abortion.

Quijada SG, Terán BM, Murias PS, Anitua AA, Cermeño JL, Frías AB.

Clin Microbiol Infect. 2012 Jun;18(6):533-8.

ABSTRACT:

Q fever, caused by Coxiella burnetii, may result in abortions in infected animals and pregnant women. However, the role that Q fever plays in spontaneous abortions is still unknown. This study examined the association between Q fever serology and abortion in a region where Q fever is endemic. A case-control population-based study was conducted in General Yagüe Hospital (Burgos area, Spain) between June 2009 and July 2010. A total of 801 samples from 500 pregnant women were tested, of whom 273 had a spontaneous abortion and 227 gave birth. IgG and IgM antibody titres against Q fever were determined in their two phases (I and II) by immunofluorescence assay. Seropositivity (phase I IgG ≥1:16 or phase II IgG ≥1:80) was detected in 88/273 (32.2%) cases and 53/227 (23.3%) controls; p <0.01, OR 1.5, 95% CI 1.0-2.3. Seropositivity for both phases of IgG, compatible with recent or persistent infection, was detected in 55 (20.1%) vs 22 (9.7%); p <0.001, OR 2.3, 95% CI 1.3-3.9. High phase II IgG antibodies compatible with active or recent infection (titres ≥1:160) were detected in 27 (9.6%) vs 7 (3.1%); p <0.002, OR 3.4, 95% CI 1.4-8.0, respectively. Q fever was diagnosed in 14 (5.1%) cases. The risk of abortion associated with serological markers of active or recent Q fever in pregnant women was measurable and noticeable in this population, and accounted for 12% (95% CI 4-21%).

GENOTYPIC ANALYSIS OF VARIOUS HUMAN *COXIELLA BURNETII* ISOLATES REVEALED A STRAIN-SPECIFIC EFFECT OF *COXIELLA BURNETII* ON PREGNANCY

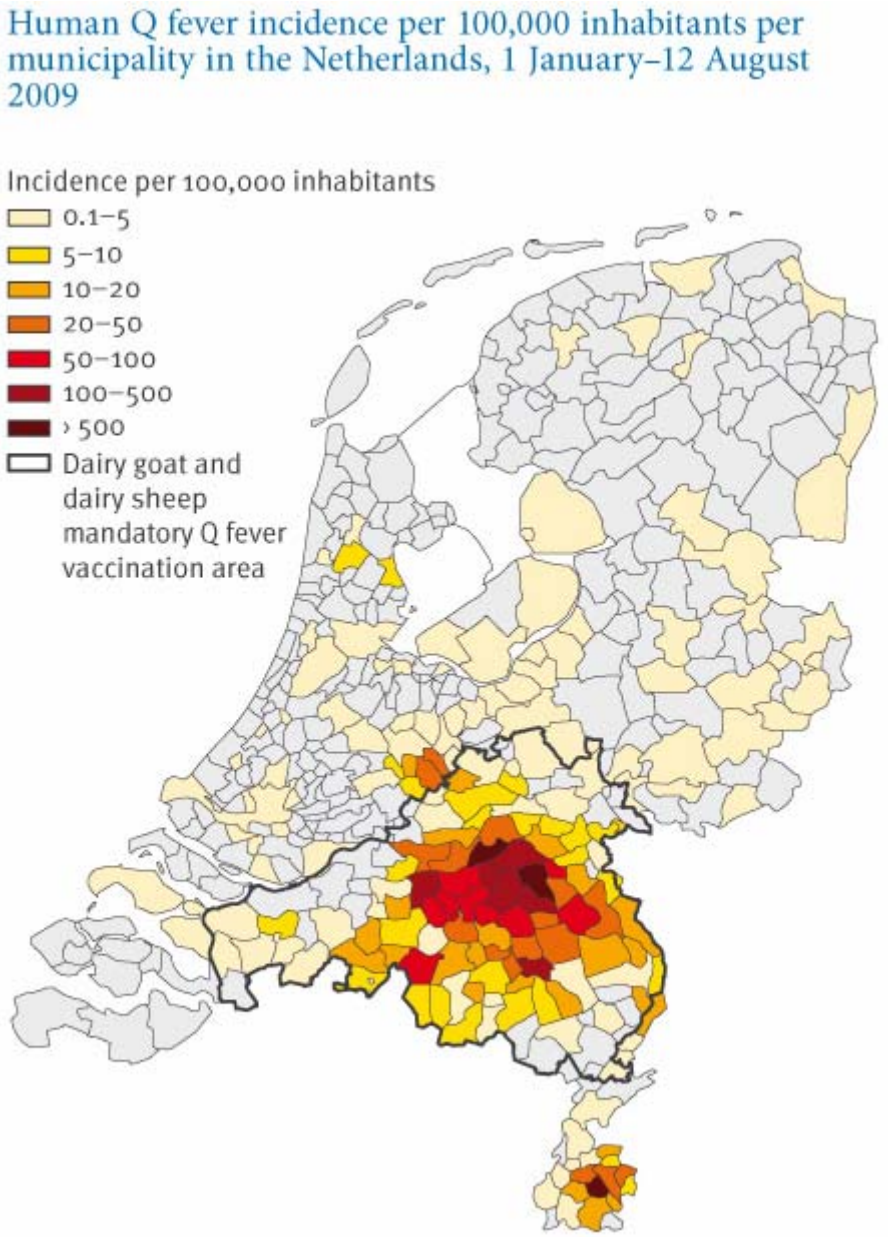
Emmanouil Angelakis[1], Felicetta D'Amato[1], Hervé Richet[1], Jean-Marc Rolain[1], Didier Raoult[1]*
URMITE – UMR CNRS, IRD, INSERM, Aix Marseille Université, Faculté de Médecine, 27 Bd Jean Moulin, 13005 Marseille, France.

Abstract

Acute Q fever is a cause of fetal morbidity in France and long-term cotrimoxazole therapy (≥5 weeks) was associated with a living newborn (p<0.0001). Genotypic analysis of various human *C. burnetii* isolates showed that the QpDV plasmid was more frequent in the placenta than the other types of plasmids (p=0.05).

Screening for *Coxiella burnetii* infection during pregnancy: pros and cons according to the Wilson and Jungner criteria. Munster JM, Steggerda LM, Leenders AC, Aarnoudse JG, Hak E. Euro Surveill. 2012 Jan 19;17(3):20061.

Abstract: In Europe the incidence of human Q fever has dramatically increased over the previous years. Untreated infections with Coxiella burnetii, the causal agent of Q fever, have been associated with both obstetric and maternal complications. The majority of pregnant women with a C. burnetii infection remain asymptomatic, hence screening could be of value to prevent unwanted outcomes in this high-risk group. We applied the updated Wilson and Jungner criteria to review the evidence for routine screening for C. burnetii infection during pregnancy. Since much uncertainty remains about the incidence, clinical consequences, diagnostics and treatment of C. burnetii infection during pregnancy, routine screening for C. burnetii infection during pregnancy should not be recommended. Rigorous studies to assess the effectiveness of C. burnetii screening are warranted.



OUR CONCLUSION
Q FEVER AND PREGNANCY

- *C.burnetii* in an aborting agent in mammals and humans
- They may be a strain specificity
- The only published work on Netherland is based on patients treated by antibiotics (erytromycin here)

EXPERT Vs CONSENSUS

Expert What is an expert?

Consensus - **E-CDC**
- **Dutch group**

Expert on acute Q fever

Dutch on acute Q fever - conclusion

Expert on Q fever and pregnancy

« consensus » on pregnancy - conclusion

Expert on « chronic Q fever »

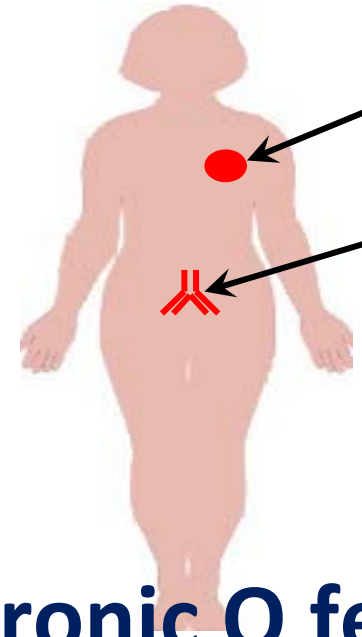
- In general
- Endocarditis
  - Diagnosis
  - Treatment
  - Prevention
- Vascular infection
- Others

Dutch consensus on « chronic Q fever »

Conclusion

3 months – 3 years
After primoinfection
(symptomatic or not)

High antibodies



Valvulopathy
→ endocarditis

Aortic Aneurisms
And
Vascular prosthesis

→ vascular infection

Chronic Q fever

Misleading based on pathophysiology theory!

Correlation of plasmid type and disease caused by Coxiella burnetii.
Samuel JE, Frazier ME, Mallavia LP. Infect Immun. 1985 Sep;49(3):775-9.

Serological evaluation of O fever in humans: enhanced phase I titers of immunoglobulins G and A are diagnostic for Q fever endocarditis.
Peacock MG, Philip RN, Williams JC, Faulkner RS.
Infect Immun. 1983 Sep;41(3):1089-98.

CHRONIC Q FEVER

Prevalence of various forms

	N° of identified cases (n=313)	%	
Endocarditis	229	73	
Vascular infection	25	8	
Pregnancy (mothers and babies)	20	6	
Chronic hepatitis	8	3	?
Osteoarticular infection	7	2	PCR
Chronic pericarditis	3	1	Rare
Adenopathies	1	<1	?
Splenic pseudotumor	1	<1	?
Lung pseudotumor	1	<1	?
Chronic neuropathy	1	<1	?
No identified foci	6	2	_?

The name chronic Q fever is misleading

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Expert What is an expert?

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« consensus » on pregnancy - conclusion

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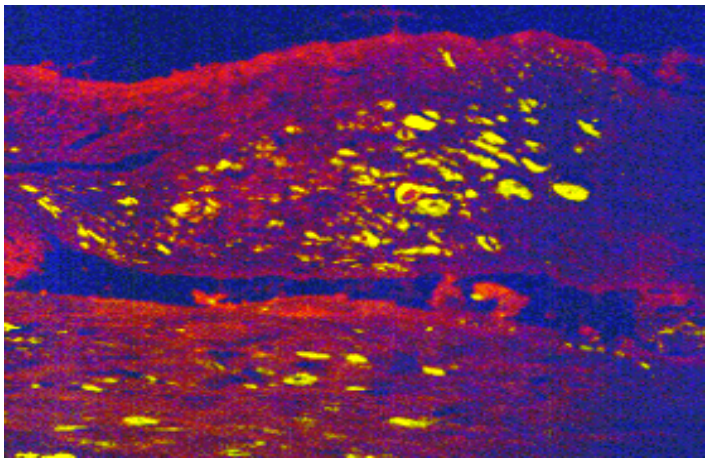
- In general
- Endocarditis → - Diagnosis
  - Treatment
  - Prevention
- Vascular infection
- Others

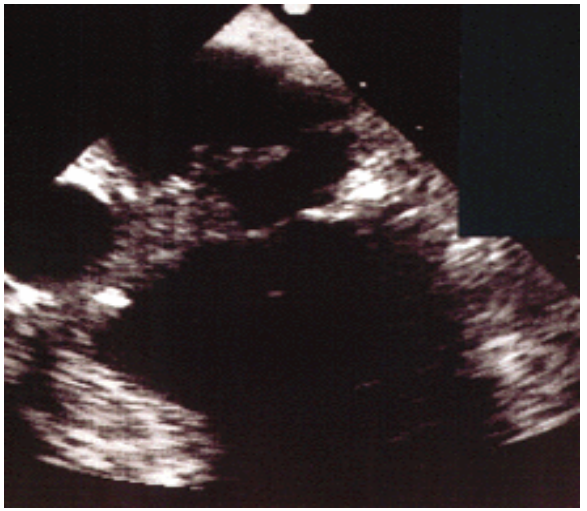
Dutch consensus on « chronic Q fever »

Conclusion

ENDOCARDITIS

- "Culture negative endocarditis"
- In patients with previously known valvulopathy +++
- In immunocompromised patients
- Atypical presentation (fever and vegetations are lacking)
- Mean diagnostic delay: 12 month
- Prognosis: 23 % of cases are fatal
  - Marseilles 1984: 65 %
  - Marseilles 1997: 5 %
  - Marseilles 2004: 2.5%





ENDOCARDITIS

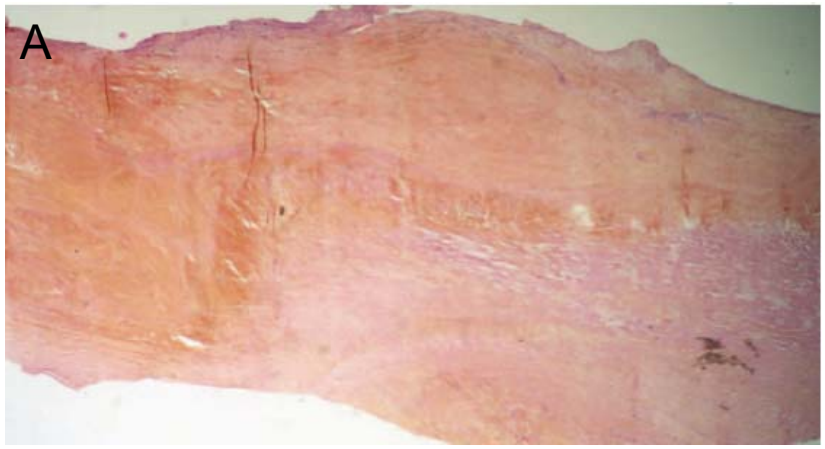
Clinical presentation of 15 cases Q fever endocarditis diagnosed in 1984 and in 2001

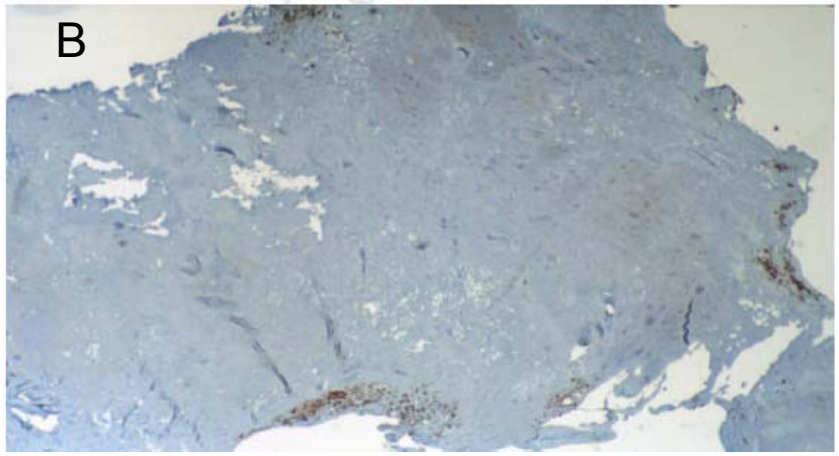
	1984	2001	P value
Diagnostic delay (month median)	18	5,7	<0.01
Cardiac failure	9	3	<0.05
Hepatomegaly	12	5	<0.01
Splenomegaly	7	4	
Increased liver enzymes	7	3	
Thrombocytopenia	7	6	
ESR > 50	15	10	
Fever (any episode)	11	10	
Valvular replacement	7	10	
Deaths within 3 years after diagnostic	6	0	<0.01

Houpikian P. et al. Changing clinical presentation of Q fever endocarditis.

Clin Infect Dis. 2002 ;34:E28-31.

Histology (A) and immunochemistry (B) of a patient with Q fever endocarditis. Note the lack of vegetation. This valve was considered not infected on gross examination and on echocardiography.





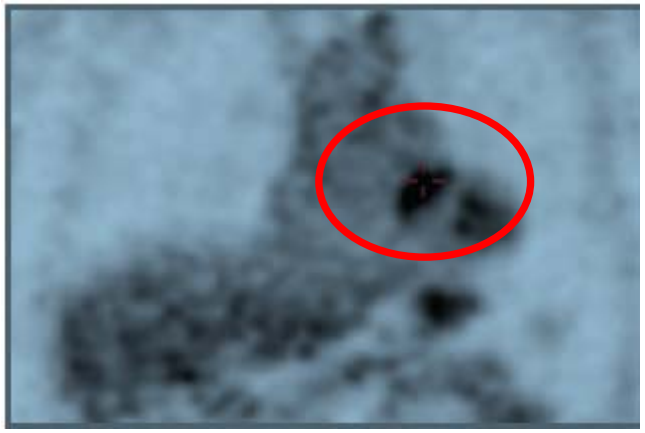
Cardiac valves in patients with Q fever endocarditis: microbiological, molecular, and histologic studies.
Lepidi H, Houpikian P, Liang Z, Raoult D.
J Infect Dis. 2003 Apr 1;187(7):1097-106

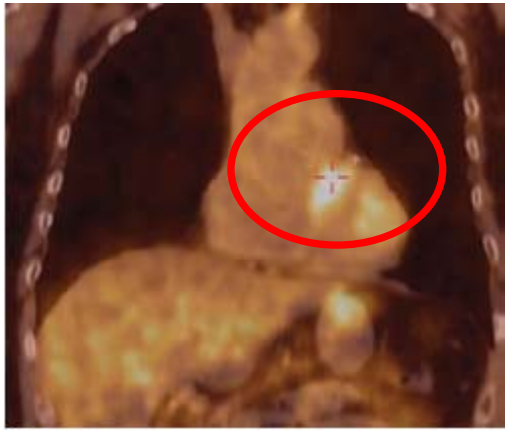
Q fever endocarditis: a surgical view and a word of caution.
Mesana TG, Collart F, Caus T, Salamand A.
J Thorac Cardiovasc Surg. 2003 Jan;125(1):217-8.

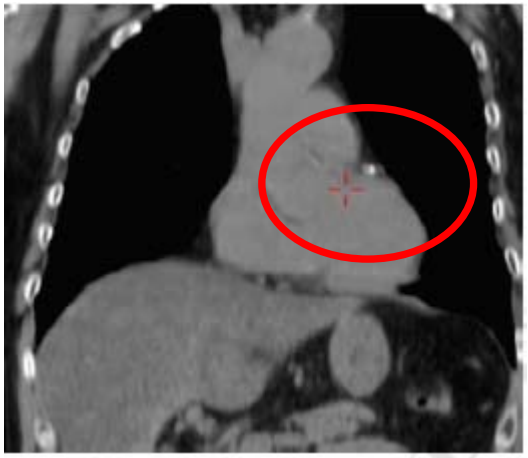
ENDOCARDITIS DIAGNOSED ON VALVE FROM MARSEILLE SEND TO THE LAB

- Between 2000 and 2012 => 20 / 3 500 valves
- Only 11 were tested and diagnosed before! By serology
- In 7 cases the serum was send the very same day (preoperative serum)
- In 2 cases after the PCR result

A





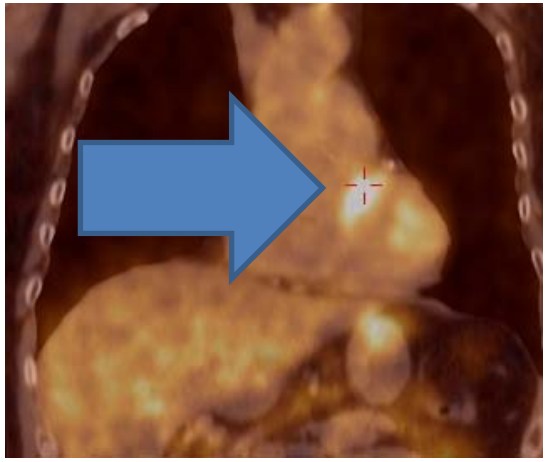


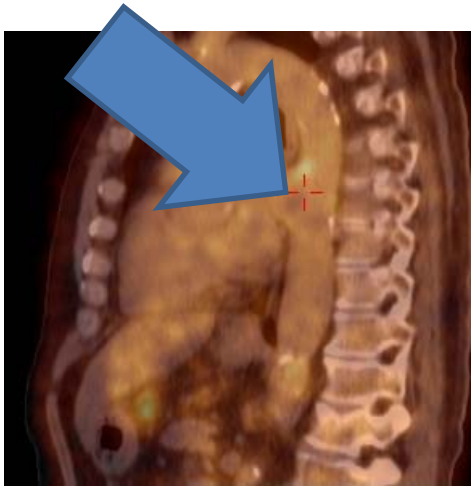
Fixation of aortic valve in a patient with Q fever endocarditis without evidence of endocarditis on echocardiography

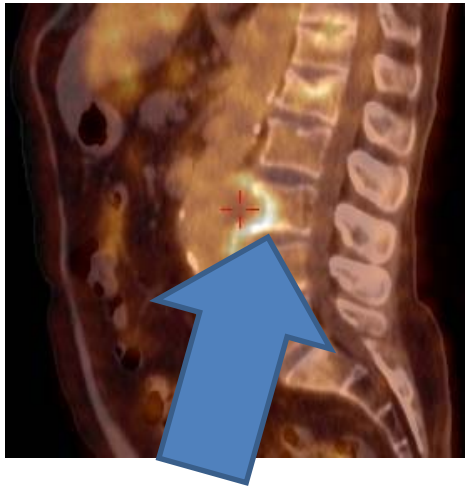
Scintigraphy CT-Scan

F-18 FDG PET scan and Q fever endocarditis

B







Aortic valve

Acuted elevated antibodies

Thoracic aortic aneurysm

Lombar aortic aneurysm with spondylodiscitis

Data of 2009 (1)

- Inclusion of the patients of 2009 according to two criteria
  - The 1st positive serology in 2009
  - Result of a known echocardiography
- Classification in function: - Duke criteria
  - Values of serology
  - Presence or not of an endocarditis
- 172 patients included
- 41 certaines
- 15 possibles

Completely different in French Guyane

IgG phase I	<800	800	1600	3200	>3200	Total
Possible	4	2	6	2	1	15
Certaine	0	9	8	7	17	41
Total	31	53	41	23	24	172
PPV		37 %	59 %	57 %	75 %	

DUTCH REPORT

CHRONIC Q FEVER: REVIEW OF THE LITERATURE AND A PROPOSAL OF NEW DIAGNOSTIC CRITERIA

Wegdam-Blans MC, Kampschreur LM, Delsing CE, Bleeker-Rovers CP, Sprong T, van Kasteren ME, Notermans DW, Renders NH, Bijlmer HA, Lestrade PJ, Koopmans MP, Nabuurs-Franssen MH, Oosterheert JJ; Dutch Q fever Consensus Group.

J Infect. 2012 Mar;64(3):247-59.

Follow-up of 686 patients with acute Q fever and detection of chronic infection.

van der Hoek W, Versteeg B, Meekelenkamp JC, Renders NH, Leenders AC, Weers-Pothoff I, Hermans MH, Zaaijer HL, Wever PC, Schneeberger PM.

Clin Infect Dis. 2011 Jun 15;52(12):1431-6.

Chronic q Fever detection in the Netherlands

Clin Infect Dis. 2011 Dec;53(11):1170-1.

Same cut of (**1024**/800) and **PCR**

COXIELLA BURNETII INFECTION AMONG BLOOD DONORS DURING THE 2009 Q-FEVER OUTBREAK IN THE NETHERLANDS.

Hogema BM, Slot E, Molier M, Schneeberger PM, Hermans MH, van Hannen EJ, van der Hoek W, Cuijpers HT, Zaaijer HL.

Transfusion. 2012 Jan;52(1):144-50.

CONCLUSION:
In the area with highest incidence during a large Q-fever outbreak, 3 of 1004 blood donations contained C. burnetii DNA (0.3%; 95% confidence interval, 0.1%-1.0%). A total of 66 of 543 (12.2%) donors tested positive for anti-Coxiella IgG. Ten seroconversions were detected, resulting in an incidence of 5.7% per year, which is more than 10-fold higher than the local number of reported clinical cases (0.47% per year).

0,3 % of PCR positive in asymptomatic cases!

Q PCR

- Discrepancies among laboratories
  - Some team report positive PCR in asymptomatic patients or years after infection
  - Our team find positive PCR only during the early phase of acute infection and during chronic infection when antibodies anti phase I IgG are between 1/800 and 1/6400
- Indications
  - Acute cases negative for IgM (pharyngeal swabs):
  - Suspicion of chronic infection with Ig anti phase I: IgG $\geq$ 800
  - Use IS IIII (7 to 20 copies) as a target
  - Increased used of threat samples

Molecular detection of Coxiella burnetii in the sera of patients with Q fever endocarditis or vascular infection.Fenollar F, Fournier PE, Raoult D. J Clin Microbiol. 2004 Nov;42(11):4919-24.

Fournier PE, Raoult D. Comparison of PCR and serology assays for early diagnosis of acute Q fever.J Clin Microbiol. 2003 Nov;41(11):5094-8

Rolain JM, Raoult D. Molecular detection of *Coxiella burnetii* in blood and sera during Q fever. QJM. 2005 ;98:615-7.

Being careful with PCR to avoid erroneous discoveries. Raoult D. Scand J Infect Dis. 2011 May;43(5):323-4.

HOW TO BE EFFICIENT IN DETECTING Q FEVER IE

Testing at risk patients with

- Fever
- Before valve replacement without evidence of IE 12/3469 (cases in our center (0.3%)) have undiagnosed IE *C.burnetii*

- Increased transaminases
- Renal insuffisency
- by testing all removed valves by 16Sr DNA (Switzerland, Lyon, Netherland) including these with other microorganisms (Marseille, Netherland)

Definition of Q Fever endocarditis Chronic Q fever:
Raoult D. Expert opinion versus literature analysis and consensus. J Infect. 2012 Apr 23

A. Definite new criterion

Positive culture, PCR, or immunochemistry of a cardiac valve.

B. Major criteria

· Microbiology : positive culture or PCR of the blood or an emboli or serology with IgGI antibodies **> 6400**

· Evidence of endocardial involvement :

- Echocardiogram positive for IE : 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 valve; or new valvular regurgitation (worsening or changing of pre-existing murmur not sufficient).
- **Pet-scan** showing a specific valve fixation and ormycotic aneurism.

C. Minor criteria

- Predisposing heart condition (know or found on echography)
- Fever, temperature > 38°C
- Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm (see at Pet-scan), intracranial hemorhage, conjunctival hemorrhages, and Janeway's lesions.
- Immunologic phenomena : glomerulonephritis, Osler's nodes, Roths spots, or rheumatoid factor.
- Serological evidence : IgGI antibodies **> 800 <6400**

Diagnosis definite

1) 1A criterion
2) 2B criteria
3) 1B criterion, and 3C criteria **(including 1 microbiology evidence, and cardiac predisposition)**

Diagnosis possible

1) 1B criterion, 2 C criteria **(including 1 microbiology evidence, and cardiac predisposition)**
2) 3C criteria **(including positive serology, and cardiac predisposition)**

SCORE *LI ET AL.*

Tableau 2.
Critères de Duke (modifiés) pour le diagnostic d'endocardite infectieuse (EI).

Critères majeurs
Hémocultures positives pour une EI:
Micro-organismes typiques pour une EI dans 2 hémocultures séparées: *Streptococcus viridans, Streptococcus bovis*, bactéries du groupe HACEK[1], *Staphylococcus aureus*; ou *enterococci* aquis dans la communauté, en l'absence d'un foyer infectieux primaire; ou
Micro-organismes non-typiques pour une EI mais isolés dans des hémocultures positives persistantes (>12 heures ou ≥3/3)
1 hémoculture positive pour *Coxiella burnetii* ou un titre d'anticorps IgG antiphase I >1:800
Evidence d'une atteinte de l'endocarde
Echocardiaque positif pour une EI (*échocardiaque trans-œsophagien recommandé chez des patients avec valves prothétiques, chez ceux définis comme EI possibles sur la base des critères cliniques ou qui ont une EI compliquée*) définit comme suit: Masse oscillante intracardiaque sur une valve, sur le trajet d'un reflux, sur du matériel prothétique ou abcès ou nouvelle déhiscence de valve prothétique
Nouveau souffle d'insuffisance valvulaire (*aggravation / modification d'un souffle connu ne suffisent pas*)
Critères mineurs
Facteurs cardiaques prédisposants (haut ou modéré) ou toxicomanie intraveineuse
Fièvre >38 °C
Phénomènes vasculaires: embolies artérielles, anévrismes mycotiques, pétéchies, hémorragie intracranienne ou conjonctivale, lésions de Janeway
Phénomènes immunologiques: glomérulonéphrites, nodules d'Osler, taches de Roth, facteur rhumatoïde
Hémoculture positive mais ne remplissant pas les critères majeures ou sérologie positive pour une affection active avec un germe compatible avec une EI

[1] Groupe HACEK: Haemophilus spp, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens and Kingella Kingae.
[De Li, et al. Clinical infectious disease 2000;30:633-8. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis].

New score Raoult

A. Definite criterion
Positive culture, PCR , or immunochemistry of a cardiac valve
B. Major criteria
Microbiology : positive culture or PCR of the blood or an emboli or **serology with IgG I antibodies ≥ 6400**
Evidence of endocardial involvement :
Echocardiogram positive for IE : 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 prothestic valve; or new valvular regurgitation (worsening or changing of pre-existing murmur not sufficient).
Pet-scan showing a specific valve fixation and mycotic aneurism
C. Minor criteria
Predisposing heart condition (know or found on echography)
Fever, temperature > 38
Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm (see at Pet-scan), intracranial hemorhage, conjunctival hemorrhages, and Janeway's lesions.
Immunologic phenomena : glomerulonephritis, Osler's nodes, Roths spots, or rheumatoid factor.
Serological evidence : IgG I ≥ 800 <6400

- Application of Li score and of Raoult score on 20 patients considered for the diagnosis of endocarditis: from 2011-2012

Score	EI possible	EI
Li	10/20	10/20
Raoult	6/20	14/20

Discordance :

• EI possible passage according to definite **5** (3 fixings with PET scan and 3 PCR positives on serum/blood allowed this reclassification)

• EI definite of to possible **1** (because IgG I = 3200 = major criterion for Li and mineur for Raoult)

Need to be confirmed by others

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Expert What is an expert?

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Expert on acute Q fever

Dutch on acute Q fever - conclusion

Expert on Q fever and pregnancy

« consensus » on pregnancy - conclusion

Expert on « chronic Q fever »

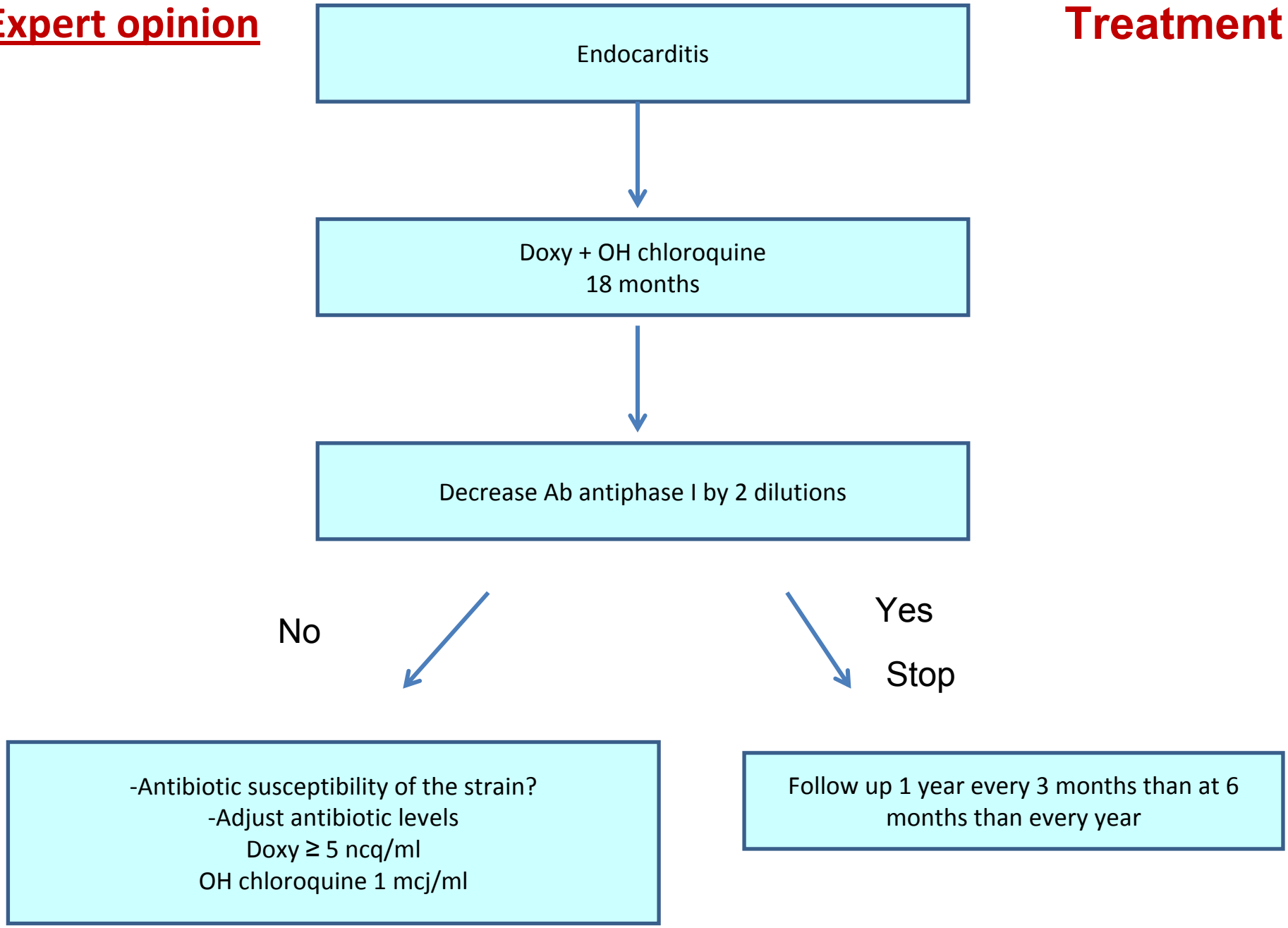
- In general
- Endocarditis - Diagnosis
  - Treatment
  - Prevention
- Vascular infection
- Others

Dutch consensus on « chronic Q fever »

Conclusion

Expert opinion

Treatment



Applicability of evidence-based practice in public health: risk assessment on Q fever under an ongoing outbreak.

Forland F, De Carvalho Gomes H, Nokleby H, Escriva A, Coulombier D, Giesecke J, Jansen A. Euro Surveill. 2012 Jan 19;17(3):20060.

Chronic Q fever

A cumulative point estimate calculated from all the studies included in this assessment, gave an overall average prevalence for chronic Q fever of **1.9%** of acute cases. Chronic Q fever can develop after, or appear as an asymptomatic infection [12,13]. The fatality rate for chronic Q fever may vary from 5% to 60% [14]. Risk factors for developing chronic disease are mainly connected to the host and include heart valve defect, heart valve prosthesis or arterial graft, aneurisms, malignancies, and immunosuppression. Medical treatment for chronic Q fever should be at **least one year** with more than one drug. The optimal treatment of chronic Q fever **is still debated** and the recommended duration of treatment varies from **one year up to a lifespan** [15]. Most authors today recommend broad-spectrum tetracyclines, preferably doxycycline in combination with hydroxychloroquine for at least 18 months [16].

15. Hellmeyer L, Schmitz-Ziegler G, Slenczka W, Schmidt S. Q-Fieber in der Schwangerschaft: Therapie und Handling des Krankheitsbildes anhand eines Fallberichtes. [Q Fever in pregnancy: a case report and review of the literature]. Z Geburtshilfe Neonatol. 2002;206(5):193-8. German. Available from: https://www.thieme-connect.com/DOI/DOI?10.1055/s-2002-34961

THIS IS NOT SERIOUS !!!

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Dutch on acute Q fever - conclusion

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Expert on « chronic Q fever »

- In general
- Endocarditis - Diagnosis
  - Treatment
  - Prevention
- Vascular infection
- Others

Dutch consensus on « chronic Q fever »

Conclusion

AVOIDING EVOLUTION ACUTE Q FEVER-ENDOCARDITIS

EXPERT

- Echocardiography

Endocarditis after acute Q fever in patients with previously undiagnosed valvulopathies. Fenollar F, Thuny F, Xeridat B, Lepidi H, Raoult D.
Clin Infect Dis. 2006 Mar 15;42(6):818-21

Risks factors and prevention of Q fever endocarditis.
Fenollar F, Fournier PE, Carrieri MP, Habib G, Messana T, Raoult D.
Clin Infect Dis. 2001 Aug 1;33(3):312-6.

- Serology 3-6-12 months

From acute Q fever to endocarditis: serological follow-up strategy.
Landais C, Fenollar F, Thuny F, Raoult D.
Clin Infect Dis. 2007 May 15;44(10):1337-40

Duval, Clin Inf Dis, 2006

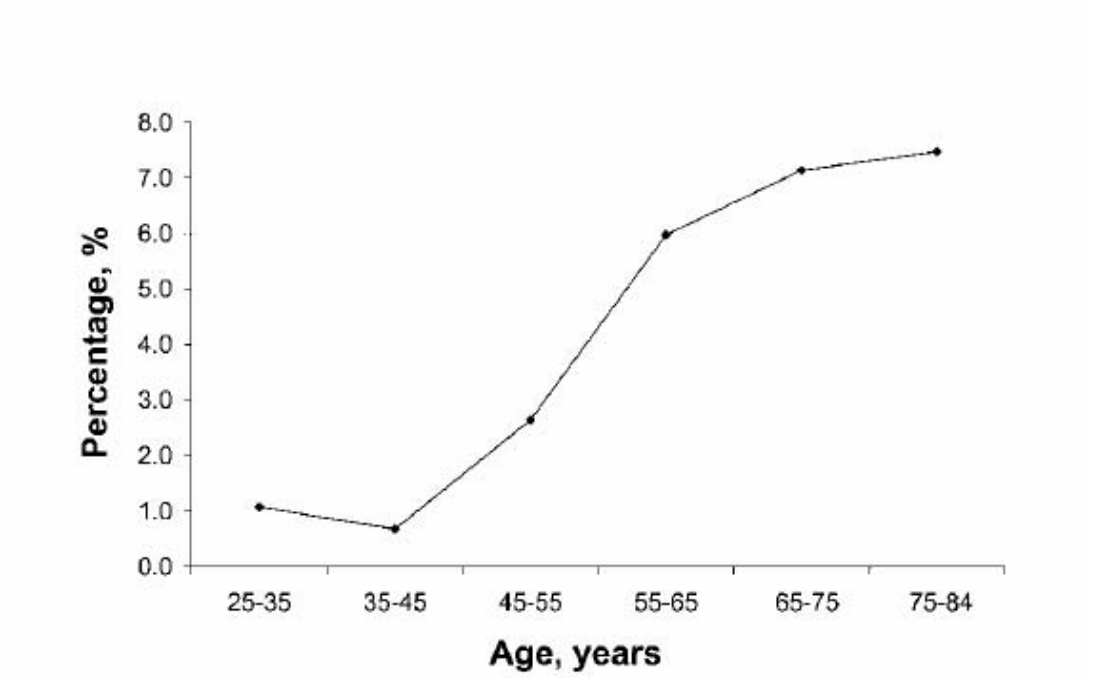


Figure 1. Age-specific prevalence of a predisposing cardiac condition among French adults (age, 25–84 years).

PREVENTION OF Q FEVER ENDOCARDITIS

Limonard GJ, Nabuurs-Franssen MH, Dekhuijzen PN, Groot CA.

Lancet Infect Dis. 2011 Feb;11(2):82-3

134 patients	Trace	Mild	Moderate	Severe
Mitral regurgitation	50	15	7	2
Aortic regurgitation	9	10	4	0
Aortic stenosis	0	2	0	0
Mitral stenosis	0	0	1	0

10 %

In fast 10% at **risk** in this population: 50 year old men

Table 2. Valvulopathy at screening echocardiography*
Severity of valvular defects were classified according to the American Society of Echocardiography guidelines, 2003.
*Multiple valvulopathies are possible for a patient.

Find 37% valvulopathies! > not useful

Chronic q Fever detection in the Netherlands

Raoult D, Million M, Thuny F, Carrieri P.

Clin Infect Dis. 2011 Dec;53(11):1170-1.

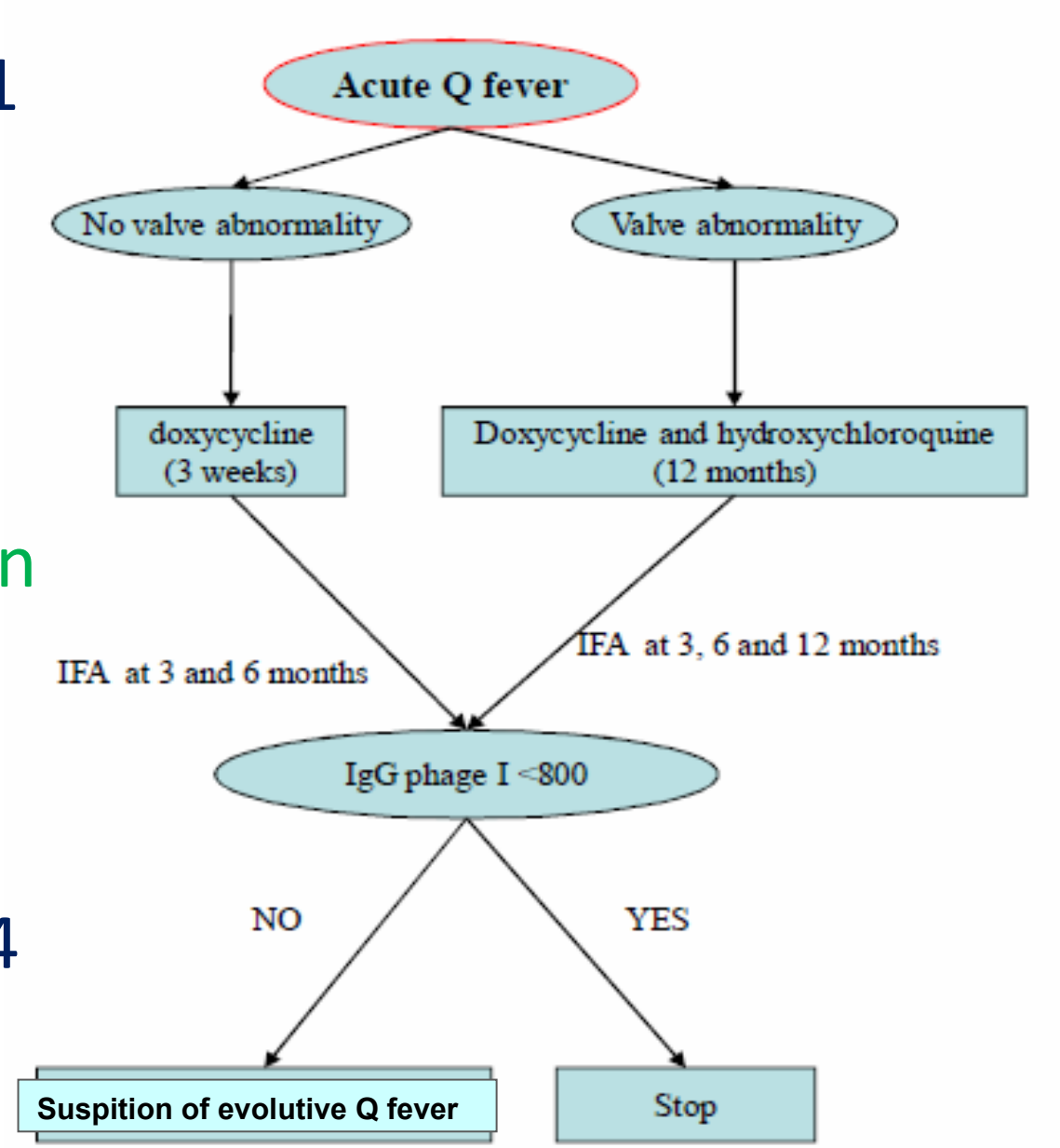
The valvulopathies predisposing patients to Q fever endocarditis are, first, prosthetic valves (which are present in 0.5% to 1% of the population in France) [5]; then, aortic bicuspidy [6] (0.5%–2% of the population); more rarely, mitral valve prolapse (0.6%–2.4% of the population) [7, 8]; and even more rarely, moderate aortic or mitral leaks (3% of the population) [9]. It is not true that more than 50% of controls or patients with acute Q fever have 1 or more of these valvular lesions. Higher risk for aortic bicuspidy 19.06 (95% CI [4.29–84.63]), followed by 4.23 (2.08–8.58) for the mitral valve prolapse and 20.06 (10.09–39.87) for a moderate mitral insufficiency.

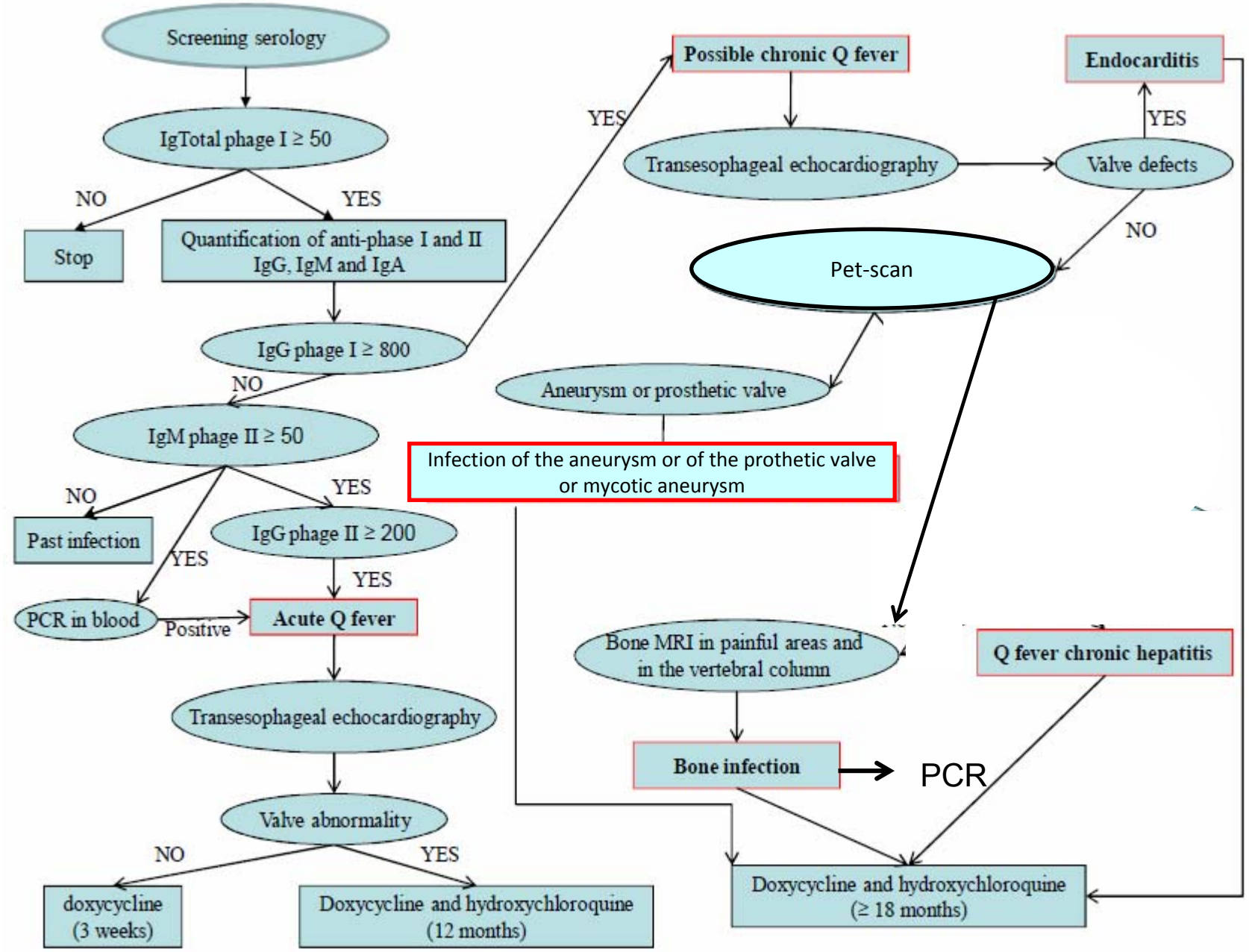
PREVENTION OF INFECTIOUS ENDOCARDITIS

Since 2001

Doubling person onselling in 2004

Since 2004




Screening serology
IgTotal phage I ≥ 50
NO
YES
Stop
Quantification of anti-phase I and II IgG, IgM and IgA
IgG phage I ≥ 800
NO
YES
IgM phage II ≥ 50
NO
YES
Past infection
IgG phage II ≥ 200
YES
YES
PCR in blood
Positive
Acute Q fever
Transesophageal echocardiography
Valve abnormality
NO
YES
doxycycline (3 weeks)
Doxycycline and hydroxychloroquine (12 months)
Possible chronic Q fever
Transesophageal echocardiography
Endocarditis
YES
Valve defects
NO
Pet-scan
Aneurysm or prosthetic valve
Infection of the aneurysm or of the prothetic valve or mycotic aneurysm
Bone MRI in painful areas and in the vertebral column
Q fever chronic hepatitis
Bone infection
PCR
Doxycycline and hydroxychloroquine (≥ 18 months)

ASK DUTCH CONSENSUS

- No echocardiography
- Serology at 6 months

EXPERT Vs CONSENSUS

Expert What is an expert?

Consensus - **E-CDC**
- **Dutch group**

Expert on acute Q fever

Dutch on acute Q fever - conclusion

Expert on Q fever and pregnancy

« consensus » on pregnancy - conclusion

Expert on « chronic Q fever »

- In general
- Endocarditis
  - Diagnosis
  - Treatment
  - Prevention
- Vascular infection
- Others

Dutch consensus on « chronic Q fever »

Conclusion

Eur J Clin Microbiol Infect Dis (2007) 26:635–640
DOI 10.1007/s10096-007-0357-6

ARTICLE

Coxiella burnetii infection of aortic aneurysms or vascular grafts: report of 30 new cases and evaluation of outcome

E. Botelho-Nevers · P.-E. Fournier · H. Richet · F. Fenollar · H. Lepidi · C. Foucault · A. Branchereau · P. Piquet · M. Maurin · D. Raoult

Published online: 13 July 2007

Abstract Q fever is a zoonotic disease caused by *Coxiella burnetii*. Polymorphic, the disease may present as an acute or chronic infection. Vascular infections are the second most common form of chronic Q fever, following endocarditis. Herein, we studied the outcome of 30 new cases of aortic infection caused by *C. burnetii* using uni- and multivariate analyses. The outcome of ten cases previously reported by our team was also updated. Of these 40 patients, 32 had a follow-up of ≥3 years. Among them, the overall mortality was of 25% (8/32). Vascular rupture was significantly and independently (multivariate P=0.03) associated with a lethal issue, whereas vascular surgery was significantly associated with recovery (uni- and multivariate P<0.01). Our findings demonstrate the critical importance of surgery in the management of *C. burnetii* vascular infections.

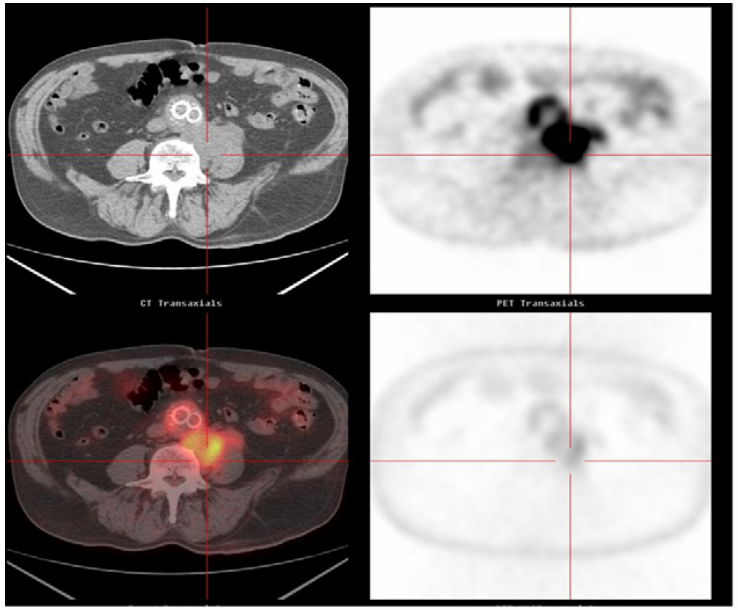
Introduction

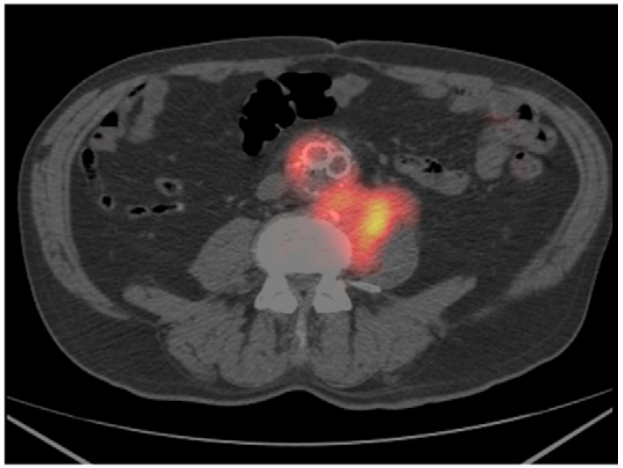
Q fever is an ubiquitous zoonosis caused by *Coxiella burnetii* (*C. burnetii*). This bacterium is a short and pleomorphic, strictly intracellular bacillus [1]. It is highly infectious and is currently classified in the category B of potential warfare agents by the Center for Disease Control and Prevention [2]. The usual source of human infection is farm animals [1]. Q fever is characterized by its clinical polymorphism and develops as acute infections, some of which will evolve to chronic forms [1, 3]. Acute and

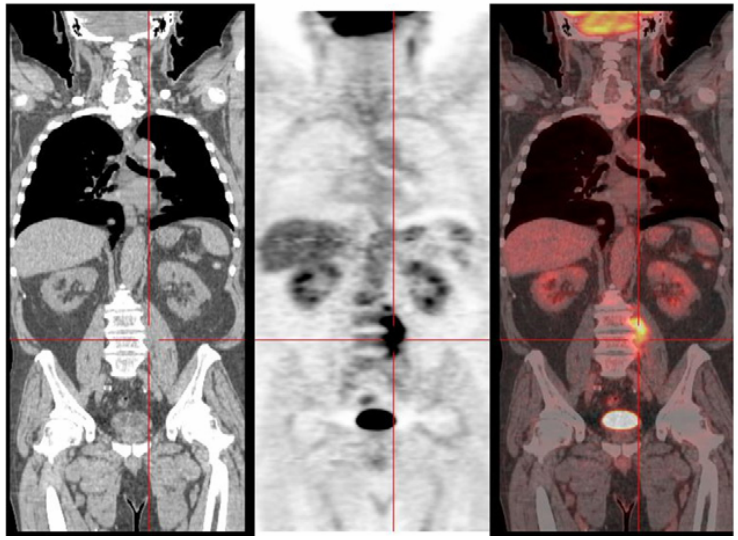
Relevance of the positron emission tomography in the diagnosis of vascular graft infection with Coxiella burnetii.

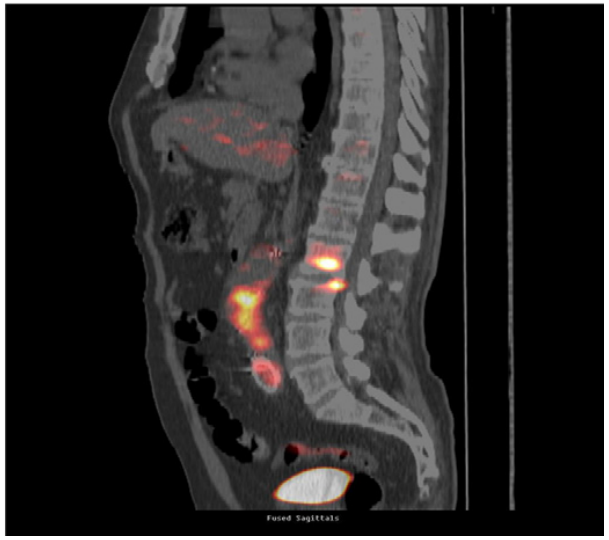
Merhej V, Cammilleri S, Piquet P, Casalta JP, Raoult D.

Comp Immunol Microbiol Infect Dis. 2012 Jan;35(1):45-9.









A FDG-PET CT scan demonstrates an increased radiotracer accumulation in the aortic abdomen and in the lower lumbar spine leading to a diagnosis of undercurrent active infection

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Dutch on acute Q fever - conclusion

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« consensus » on pregnancy - conclusion

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- In general
- Endocarditis
  - Diagnosis
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  - Prevention
- Vascular infection
- Others

Dutch consensus on « chronic Q fever »

Conclusion

Chronic Q fever

Prevalence of various forms

	N° of identified cases (n=313)	%	
Endocarditis	229	73	
Vascular infection	25	8	
Pregnancy (mothers and babies)	20	6	
Chronic hepatitis	8	3	?
Osteoarticular infection	7	2	PCR
Chronic pericarditis	3	1	Rare
Adenopathies	1	<1	?
Splenic pseudotumor	1	<1	?
Lung pseudotumor	1	<1	?
Chronic neuropathy	1	<1	?
No identified foci	6	2	_?

The name chronic Q fever is misleading

EPIDEMIOLOGY

SEROPREVALENCE AND SEROLOGY

Different techniques with:

- different antigens
- different purification
- adsorption of RF (remove IgG) or not
- prozone phenomenon (several dilution)

Cut off determine positive cases

-No cut for seroprevalence! by definition

- Usable with much caution, to compare 2 countries or two populations in the same country.

NETHERLAND Q FEVER

-Transfusion study make in the highly prevalent area of 84.000 inhabitant an incidence of 5.7% /year (10 x diagnosed cases).10 000 infected cases consisting of ¼ of Netherland cases, 40.000 cases of infection.

- Predisposing valvular diseases ≈ 1.5 – 2 % = if 50 % have IE
Expecting 300 cases of IE caused by *C.burnetii* in Holland until 2019!

EXPERT Vs CONSENSUS

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« consensus » on pregnancy - conclusion

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- Others

Dutch consensus on « chronic Q fever » Vs my opinion

Conclusion

Dutch consensus guideline (38)	
Proven : Any of the following ! - Positive PCR for Coxiella burnetii in serum, plasma, or tissue in the absence of acute Q fever - IFA phase I titer ≥1,024 with definite endocarditis according to the revised Duke criteria (21) - Indication of vascular infection on PET/CT, CT, MRI, or ultrasound testing	**Proven :** Does not make sense you need to have proof of infection AND (not or) microbiological evidence
Probable : IFA phase I IgG titer ≥1,024 and any of the following clinical manifestations : - Valvulopathy not meeting the criteria of endocardial involvement of the major modified Duke criteria (39) - Aneurysm, vascular prosthesis or prosthetic valve without signs of infection on PET/CT,CT,MRI, or ultrasound testing - Signs of possible chronic Q fever infection of noncardiac or vascular origin on PET/CT, CT or ultrasound testing -Pregnancy - Clinical symptoms of chronic infection (i.e., fever, night sweats, weight loss, hepatosplenomegaly) -Histopathologic proven granulomatous inflammation - Immune disorder	**Probable :** (some positive have no endocarditis or identified infection) -This is valuable only if other factor actively tested (Rheumatoïd factor mycotic aneurism and negative) - Does not make sense for hepatitis – No chronic hepatitis described -I don't know what pregnancy is doing here. -The problem of pregnancy is acute Q fever in the 3 first months -I don't know what granulomateous infection is linked to chronic Q fever - The relation between immune disorder and *C. burnetii* is strange
Possible : IFA phase I IgG titer ≥1,024 without clinical manifestations as described above	Everything is possible!

TAKE HOME LESSON

➢ Do not define a disease by a biologic test only, here or elsewhere. There are false positive and false negative.

➢ « Chronic Q fever » is not a good name borne on a false hypothesis of virulence plasmid for chronic infection

Correlation of plasmid type and disease caused by Coxiella burnetii.
Samuel JE, Frazier ME, Mallavia LP. Infect Immun. 1985 Sep;49(3):775-9.

➢ Rare and complicated diseases cannot be analyzed by non-expert on littérature only!

Politics is politics and knowledge is knowledge

An expert is somebody who had work and have knowledge on a disease!