Journal of Infection (2012) **65**, 102—108

BIAM
British Infection Association

www.elsevierhealth.com/journals/jinf

COMMENTARY

Chronic Q fever: Expert opinion versus literature analysis and consensus

Didier Raoult*

Unité de Recherche sur les Maladies Infectieuses et Tropicales Emergentes, Faculté de Médecine, CNRS UMR 7278, IRD 198, IRD 198, Aix Marseille Université, 27 Boulevard Jean Moulin, 13385 Marseille cedex 05, France

Accepted 10 April 2012
Available online 23 April 2012

KEYWORD
Q fever

Summary Q fever has long been considered a rare disease. The extensive outbreak in the Netherlands generated a body of literature based solely on the consensus in the Netherlands. As a long-standing expert on Q fever, I offer my experience and recommendations to the E-CDC and the Dutch Q fever Consensus Group. My (biased) opinion is that experts deeply involved in the field continue to be useful in the management of outbreaks and can avoid decisions that produce an unfavorable progression in patients. Here, I propose that the definition of "chronic Q fever" be avoided and suggest a new score-based diagnosis for Q fever endocarditis and vascular infection.

Introduction

The consensus on the definition of Q fever is timely and raises important questions, and I would like to comment on consensus in the context of the renewed interest following the extensive Netherlands outbreak.[1] It shows that the disease definition may benefit from a readjustment. I have been working on this disease since 1984[2,3] and have created a WHO and National reference center on this disease. Currently, meta-analysis or Cochrane library studies postulate that a careful analysis of the literature may substitute for expert opinion. This may be true in some but not all cases. In relatively rare or sporadic diseases, random studies have not been performed, and I believe that reference centers and individual experts are critical in the management of outbreaks. Here, I would like to use the Netherlands case as a lesson to provide necessary clarification by adding an expert opinion.[1] Currently, 8 persons are partly devoted to this topic in my laboratory, and to date, we have tested more than 200,000 samples for this purpose (see Table 1). Since 1989, I have personally consulted 800 individuals suffering from Q fever, and I have authored 182 of all 1183 papers (15%) ever published on Q fever or *Coxiella burnetii* (source: ISI Web of Science, 2012)! Therefore, I believe that my experience may help the scientific community to better understand this disease.

Definition of acute Q fever

There exists an ambiguity on the definition of the forms known as chronic and acute Q fever that may confound the interpretation of the literature. In many aspects, Q fever

* Tel.: +33 4 91 32 43 75; fax: +33 4 91 38 77 72.
E-mail address: Didier.raoult@gmail.com

0163-4453/$36
doi:10.1016/j.jinf.2012.04.006

Table 1 Q fever activity in 2011 of the French National Reference Centre.

Microbiology	
Serology	
Tested sera	**14,648**
Quantification (IgGI MA phase I and II)	1769
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[a]	**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
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

[a] This includes follow up and there are more file than patients.

appears similar to tuberculosis (TB) with a primo-infection and later manifestation localized on different organs.[4] Primo-infection by *C. burnetii*, also called acute Q fever, can be completely asymptomatic (50—90% of the cases are reported as TB primo-infection) or commonly arises with minor clinical signs; however, the symptoms can be severe in certain cases.[4,5] The procedure necessary to diagnose acute Q fever makes it possible to identify, at best, between 5 and 10% of the patients that are actually infected by *C. burnetii*. Recent work during the epidemic in Holland[6] confirmed these data by demonstrating that only 10% of the patients who presented a seroconversion were diagnosed as having clinically diagnosed acute Q fever.

There are multiple clinical forms of acute Q fever, and the form is dependent on the strain,[7] as recently described for TB.[8] It is clear that certain strains are more commonly associated with symptomatic acute infections in humans, as observed in animals,[7,9,10] than are other strains. Surprisingly, it was observed during the extensive epidemic in Holland that no abortions were reported.[11] Moreover, most cases in this outbreak were caused by a single strain,[12,13] and therefore, the spectrum of the infection in the Netherlands may be interpreted accordingly. The genome of this strain has not been released, and I have failed to obtain the strain to compare it to other strains in our genomotyping study.[14] Fortunately, this strain appears to be identical to a genotype that was previously isolated in France and Germany and is available for further study.

Following this observation, in a recent work,[13] we showed that all strains do not have the same link to human abortion, and strains (circulating in France and Spain) with a QPVD plasmid type are more commonly associated with abortions than other strains. In the absence of information on the strains that circulate during an epidemic, the management of pregnant women is complex and must be handled carefully. In pregnant women, the number of abortions and prematurities related to *C. burnetii* during acute Q fever in France is high,[15] which may be related to the circulation of local strains. Moreover, the role of *C. burnetii* in abortion in nearly all studied mammals leaves little doubt regarding the role of this bacterial species as an agent of abortion in humans.[4] Finally, there is clear evidence that a certain number of abortions are attributed to *C. .burnetii* because one can find the pathogen in the dead embryo and placenta![4] The incidence of *C. burnetii* is difficult to evaluate because the incidence is related to the nature of the strains that circulate. We continue to recommend the prescription of cotrimoxazole throughout pregnancy up to 15 days prior to the expected full-term date.[15]

Endocarditis

All acute infections, including asymptomatic infections, can subsequently generate an endocarditis, or a vascular infection similar to TB can cause a localized infection after minor or asymptomatic primo-infection. The term chronic Q fever was initially defined based on the presence of a disease that spontaneously lasts more than six months; in practice, these are endocarditis and vascular infections as well as a few other localized diseases (e.g., pericarditis and osteomyelitis). There is an association between endocarditis and an increase in anti-phase I IgG antibodies.[3,16,17] The same association was later found in patients with vascular infection. Because endocarditis (and vascular infections)[18,19] caused by *Coxiella burnetti* is difficult to diagnose (i.e., there is no available routine culture, and it is a slowly evolving disease), serology became a key factor in the identification of this infection. Based on a limited number of samples, a titer of 800 using immunofluorescence (IF) to the phase I *C. burnetii* was considered a key factor in the diagnosis of Q fever.[18] This method was then proposed and retained as an additional major criterion in the Duke endocarditis digestic score.[20,21]

However, confusion has arisen on the part of certain persons that a high antibody titer is sufficient to define the presence of a "chronic infection".[1] This perception is not correct. For example, serologies of young patients suffering an acute Q fever, particularly when one is clinically marked, can, during the period of convalescence, reach relatively high titers that will later decrease. Such cases can show titer levels of up to 3200. As a specialist in this disease, having tested many samples, checked all of the results myself, consulted patients and answered questions