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Emmanouil Angelakis, Didier Raoult

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1 **Q fever**

2

3 Emmanouil Angelakis and Didier Raoult\*

4

5 <sup>1</sup>Unité des Rickettsies, CNRS UMR 6020, IFR 48, Faculté de Médecine, Université  
6 de la Méditerranée, 27 Bd Jean Moulin, 13385 Marseille Cedex 05, France

7

8 Corresponding author.

9 Mailing address: Unité des Rickettsies, CNRS UMR 6020, IFR 48, Faculté de  
10 Médecine, Université de la Méditerranée, 27 Bd Jean Moulin, 13385 Marseille Cedex  
11 05, France

12

13 Phone: (33) 491 38 55 17

14 Fax: (33) 491 83 03 90

15 Email: [didier.raoult@gmail.com](mailto:didier.raoult@gmail.com)

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23 **Abstract**

24 Q fever is a zoonotic disease caused by the ubiquitous pathogen *Coxiella burnetii*  
25 responsible for acute and chronic clinical manifestations. Farm animals and pets are  
26 the main reservoirs of infection, and transmission to human beings is mainly  
27 accomplished through inhalation of contaminated aerosols. This illness is associated  
28 with a wide clinical spectrum, from asymptomatic or mildly symptomatic  
29 seroconversion to fatal disease. In humans Q fever can manifest as an acute disease  
30 (mainly as a self-limited febrile illness, pneumonia, or hepatitis) or as a chronic  
31 disease (mainly endocarditis), especially in patients with previous valvulopathy and to  
32 a lesser extent in immunocompromised hosts and in pregnant women. In contrast in  
33 animals, Q fever is in most cases, strikingly asymptomatic. The definite diagnosis of  
34 Q fever is made based on a significant increase in serum antibody titers, the  
35 determination of which often requires considerable time, and therefore patients must  
36 be monitored for a certain period. The treatment is effective and well tolerated, but  
37 must be adapted to the acute or chronic pattern with the tetracyclines to be considered  
38 the mainstay of antibiotic therapy. Several actions have been proposed to prevent and  
39 reduce the animal and environmental contamination. Vaccination of animals in  
40 infected flocks, as well as in uninfected ones close to them, with an efficient vaccine  
41 can prevent abortions and shedding of the bacteria.

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## 47 **Introduction**

48 Q fever is a zoonosis caused by *Coxiella burnetii*, a small obligate intracellular  
49 gram-negative bacterium that is prevalent throughout the world (Maurin and Raoult,  
50 1999). Farm animals and pets are the main reservoirs of infection, and transmission to  
51 human beings is mainly accomplished through inhalation of contaminated aerosols.  
52 This illness is associated with a wide clinical spectrum, from asymptomatic or mildly  
53 symptomatic seroconversion to fatal disease.

54 Q fever was described in 1935 as an outbreak of febrile illness in abattoir  
55 workers in Brisbane, Australia (Derrick, 1937). Derrick examined all those who were  
56 affected and could not arrive at a diagnosis from the patients' history, physical  
57 examination, and a few investigations. As a result, he termed the illness "Q" for query  
58 fever. Later, some workers suggested that the Q stood of Queensland, the state in  
59 which the disease was first described (McDade, 1990). However, once the  
60 epidemiology of the disease became known and its status as a zoonosis established,  
61 this investigation lost favor. Subsequently, Burnet and Freeman (Burnet and Freeman,  
62 1937) isolated a fastidious intracellular bacterium from guinea pigs that had been  
63 injected with blood or urine from Derrick's patients and named it *Rickettsia burnetii*.  
64 This bacterium was morphologically and biochemically similar to other gram-  
65 negative bacteria. On the basis of cultural and biochemical characteristics, Philip  
66 (Philip, 1948) classified *R. burnetii* in a new genus, *Coxiella*, named after Herald R.  
67 Cox, who first isolated this microorganism in the United States. This genus contained  
68 only one species, *C. burnetii*. Since then, it has been isolated from several mammals  
69 and from ticks, and it may persist in the environment.

70 During the last decade our knowledge on Q fever has greatly expanded,  
71 mainly due to the identification of new clinical manifestations, the recognition of the

72 role of host factors in the expression of acute Q fever and evolution to chronic  
73 infection, and the adoption of prolonged combination antibiotic regimens for Q fever  
74 endocarditis

## 75 **Bacteriology**

76 *C. burnetii* is a small, obligate intracellular Gram-negative bacterium that  
77 cannot be grown in axenic medium. It is a small pleomorphic rod (0.2–0.4  $\mu\text{m}$  wide,  
78 0.4–1.0  $\mu\text{m}$  long) with a membrane similar to that of a Gram-negative bacterium  
79 (Maurin and Raoult, 1999). It replicates to high numbers within a parasitophorous  
80 vacuole of eukaryotic host cells, with an estimated doubling time of 20 to 45 hours  
81 (Mertens K. and Samuel, 2007). The organism may occur as a small-cell variant or  
82 large-cell variant. The small-cell variant is a compact, small rod with a very electron-  
83 dense center of condensed nucleoid filaments. The large-cell variant is larger and less  
84 electron-dense and is the metabolically active intracellular form of *C. burnetii*. It  
85 undergoes sporogenic differentiation to produce resistant, spore-like forms, the small-  
86 cell variants. These are released when the cells lyse and can survive for long periods  
87 in the environment.

88 *C. burnetii* was classified in the *Rickettsiales* order, the *Rickettsiaceae* family,  
89 and the *Rickettsiae* tribe together with the genera *Rickettsia* and *Rochalimaea*. To date  
90 based on 16S rRNA sequence analysis; the bacterium was reclassified from the order  
91 *Rickettsiales* to *Legionellales*, and falls in the gamma group of Proteobacteria. Within  
92 this proteobacteria group, the bacterium's phylogenic neighbours include *Legionellae*  
93 spp, *Francisella tularensis*, and *Rickettsiella* spp. (Raoult *et al.*, 2005).

94 *C. burnetii* possesses a small circular chromosome of approximately 5Mbp. Most  
95 isolates harbor additionally one of four previously described plasmids of 32 to 51kb in  
96 size, which carry about 2% of the genome information. Strains without a resident

97 plasmid carry instead a 16kb plasmid-like sequence integrated in the chromosome  
98 (Mallavia, 1991). The genome has a G+C content of 43 mol% and 2134 coding  
99 sequences are predicted, of which 719 (33.7%) are hypothetical, with no significant  
100 similarity to other genes in the database (Seshadri *et al.*, 2003; Hoover *et al.*, 1992).  
101 Moreover, many of the 83 pseudogenes that have been identified in *C. burnetii*  
102 contain single frameshifts, point mutations, or truncations which imply a recent origin  
103 and indicate that genome reduction is a relatively early outgoing process (Seshadri *et*  
104 *al.*, 2003). Three degenerate transposons and 20 IS elements are also identified, with  
105 21 copies of a unique IS110-related isotype IS1111, five IS30 and three ISAs1 family  
106 elements (Seshadri *et al.*, 2003).

## 107 **Epidemiology**

108 Q fever has been described worldwide except in New Zealand. From 1999 to  
109 2004, there were 18 reported outbreaks of Q fever from 12 different countries  
110 involving two to 289 people. Six outbreaks involved sheep; three involved goats; one  
111 resulted from exposure to goat manure; one from exposure to ovine manure; one  
112 involved exposure to wild animals; one involved exposure to cats and dogs; and in  
113 two outbreaks the source was unknown (Arricau-Bouvery and Rodolakis, 2005).

114 The reservoirs are extensive but only partially known and include mammals,  
115 birds, and arthropods, mainly ticks. Although over 40 tick species can be naturally  
116 infected with *C. burnetii*, they appear to not be important in the maintenance of  
117 infections in livestock or humans (Maurin and Raoult, 1999). The organism does,  
118 however, multiply in the gut cells of ticks and large numbers of *C. burnetii* are shed in  
119 tick feces. Contaminated hides and wool may be a source of infection for people  
120 either by direct contact or after the feces have dried and been inhaled as airborne dust  
121 particles. The most commonly identified sources of human infection are farm animals

122 such as cattle, goats, and sheep. *C. burnetii* localizes to the uterus and mammary  
123 glands of infected animals (Babudieri, 1959). Pets, including cats, rabbits, and dogs,  
124 have also been demonstrated to be potential sources of urban outbreaks. In North  
125 America, outbreaks of Q fever have resulted from direct and indirect contact with  
126 parturient cats (Marrie and Raoult, 2002). Outbreaks have also been reported  
127 following exposure to infected pigeon feces (Stein and Raoult, 1999).

## 128 **Routes of transmission to humans**

129 **Aerosols.** From experimental and epidemiological evidence, there is no doubt that  
130 contaminated aerosols are the major mechanism whereby *C. burnetii* is transmitted to  
131 humans (Tiggert and Benenson, 1956;Gonder *et al.*, 1979;Marrie *et al.*, 1989).

132 Persons in contact with farm animals can be infected by inhalation of contaminated  
133 aerosols from amniotic fluid or placenta or contaminated wool but also at risk are  
134 laboratory personnel who work with infected animals (Johnson, III and Kadull, 1966).

135 **Oral route.** Mammals also shed *C. burnetii* in milk, and thus, consumption of raw  
136 milk could be a source of infection (Maurin and Raoult, 1999). Although  
137 contaminated milk can be a risk factor for Q fever infection (Marmion *et al.*, 1956;  
138 Fishbein and Raoult, 1992), the evidence from experiments in which contaminated  
139 milk was fed to volunteers were contradictory (Benson *et al.*, 1963;Editorial,  
140 1950;Krumbiegel and Wisniewski, 1970). Ingestion of pasteurized cheese and tobacco  
141 smoking can be also risk factors for acquisition Q fever (Hatchette *et al.*, 2000).

142 **Percutaneous route.** Ticks transmit *C. burnetii* to domestic mammals but not to  
143 humans (Kazar, 1996).

144 **Person to person transmission.** Person-to-person transmission of *C. burnetii* is rare.  
145 Transmission of Q fever to attendants during autopsies (Harman, 1949; Gerth *et al.*,



146 1982) or infection from a patient to the hospital staff (Deutch and Peterson, 1950) can  
147 occur.

148 **Sexual transmission.** A recent report describes sexual transmission (Milazzo *et al.*,  
149 2001). Sexual transmission of Q fever has been demonstrated in mice (Kruszewska  
150 and Tylewska-Wierzbanowska, 1993) and viable *C. burnetii* has been found in bull  
151 semen (Kruszewska and Tylewska-Wierzbanowska, 1997).

152 **Age and gender.** There are several studies in which young age seems to be protective  
153 against *C. burnetii*. In a large outbreak of Q fever in Switzerland, symptomatic  
154 infection was five times more likely to occur in those over 15 years of age compared  
155 with those younger than 15 (Dupuis *et al.*, 1985). In children the sex ratio of clinical  
156 cases as well as that of infections is 1:1. The change in sex ratio at puberty can be  
157 explained by the protective role of 17- $\beta$ -estradiol in clinical expression, which has  
158 been demonstrated in mice (Leone *et al.*, 2004)

### 159 **Transmission in animals**

160 Infected ticks are probably most important in maintaining the whole cycle of  
161 *C. burnetii* (Stoker and Marmion, 1995). Ticks may play a significant role in the  
162 transmission of *C. burnetii* among the wild vertebrates, especially in rodents,  
163 lagomorphs, and wild birds (Babudieri, 1959;Lang, 1990;Marrie *et al.*, 1989). Dogs  
164 can also be infected by tick bite (Mantovani and Benazzi, 1953). Although  
165 experimental transmission of *C. burnetii* from infected to uninfected guinea pigs via  
166 tick bite has been performed with *Ixodes holocyclus*, *Haemaphysalis bispinosa*, and  
167 *Rhipicephalus sanguineus* (Maurin and Raoult, 1999), ticks are not considered  
168 essential in the natural cycle of *C. burnetii* infection in livestock (Babudieri, 1959).  
169 Ticks expel heavy loads of *C. burnetii* with their feces onto the skin of the animal host  
170 at the time of feeding.

171           Animals which live in close contact can become infected with *C. burnetii*.  
172   Sanford *et al.* described abortions that occurred in goat herds that were exposed to  
173   three goats from another herd that kidded prematurely during a fair (Sanford *et al.*,  
174   1994). Twenty one days after exposure abortions began and affected 20 to 46% of the  
175   pregnant animals in each herd. Moreover, when cows were imported into an area of  
176   endemic infection, 40% of uninfected cows became *C. burnetii* infected within 6  
177   months (Huebner and Bell, 1951).

178           Dogs may be infected by consumption of placentas or milk from infected  
179   ruminants, and by the aerosol route. Anti-phase II antibody seroprevalence was found  
180   ranging from 7 to 53% among wild brown rat populations in the United Kingdom and  
181   the authors hypothesized that wild rats may represent a major reservoir of *C. burnetii*  
182   from which domestic animals, especially cats, which are natural predators of these  
183   animals, may become contaminated (Webster *et al.*, 1995).

#### 184   **Pathogenicity**

185           A major characteristic of *C. burnetii* is its antigenic variation, called phase  
186   variation. Organisms isolated from acutely infected animals, arthropods, or humans  
187   express a wild virulent form, with smooth full length LPS named Phase I. After  
188   several passages in embryonated hen eggs or cell culture, the bacterium shifts from  
189   Phase I to an avirulent phase (Phase II), similar to the smooth to rough variation  
190   described for many *Enterobacteriaceae* (Hotta *et al.*, 2002). Phase variation is  
191   probably not a single step process, as intermediate-phase or semi-rough LPS types  
192   have been described (Vodkin and Williams, 1986; Amano *et al.*, 1987). Virulent Phase  
193   II bacteria express a truncated, rough LPS molecule and many differ in surface protein  
194   composition, surface charge and cell density (Mertens K. and Samuel, 2007).

195           The target cells of *C. burnetii* are monocytes/macrophages. Capo *et al.* showed  
196 that virulent *C. burnetii* organisms survived inside human monocytes, whereas  
197 avirulent bacteria were eliminated (Capo *et al.*, 1999). In addition, they were  
198 phagocytosed by host cells at markedly lower efficiency than avirulent variants. *C.*  
199 *burnetii* enters monocytes/macrophages, the only known target cells, by phagocytosis  
200 that differs in phase I and phase II cells. Attachment of phase I bacteria is mediated by  
201  $\alpha v \beta 3$  integrin only, whereas phase II attachment is mediated by both  $\alpha v \beta 3$  and  
202 complement receptor CR3 (Capo *et al.*, 1999). As the efficiency of CR3-mediated  
203 phagocytosis depends on CR3 activation via  $\alpha v \beta 3$  integrin, the low phagocytic  
204 efficiency observed with virulent *C. burnetii* results from the interference with  
205 integrin cross-talk and a pre-treatment of monocytes with virulent bacteria prevents  
206 CR3-mediated phagocytosis and CR3 activation. Virulent bacteria stimulate the  
207 formation of pseudopodal extensions and transient reorganization of filamentous  
208 actin, whereas avirulent agents have no effect (Meconi *et al.*, 1998). Finally, specific  
209 inhibitors of src-related kinases prevent *C. burnetii* stimulated reorganization of the  
210 cytoskeleton (Meconi *et al.*, 2001).

211           The adaptation of *C. burnetii* to intracellular life is linked with acidic pH of its  
212 phagosome and both virulent and avirulent bacteria are found in phagosomes. Acidic  
213 pH allows the entry of nutrients necessary for *C. burnetii* metabolism and also  
214 protects bacteria from antibiotics by altering their activity (Hackstadt and Williams,  
215 1981). The survival of *C. burnetii* in human macrophages is based on the control of  
216 phagocytosis and the prevention of ultimate phagosome lysosome fusion. This is  
217 based on the fact that virulent organisms are presented in phagosomes that express  
218 endosomal markers such as the mannose 6-phosphate receptor, LAMP1 and proton  
219 ATPase, but they do not acquire a marker such as cathepsin D. On the other hand,

220 avirulent agents are presented in phagosomes that colocalize with cathepsin D.  
221 Finally, defective phagosome maturation is induced by exogenous IL-10 in monocytes  
222 from patients with microbicidal competence and corrected IL-10 neutralization in  
223 patients with chronic Q fever which means that phagosome maturation and *C. burnetii*  
224 killing are linked in Q fever and are controlled by cytokines (Ghigo *et al.*, 2004).

225 Toll-like receptor 4 (TLR4) has also a role in the uptake of virulent *C.*  
226 *burnetii*, since it is involved in the recognition of lipopolysaccharide, and in  
227 membrane ruffling induced by phase I lipopolysaccharide (Honstette *et al.*, 2004).  
228 TLR2 is also involved in *C. burnetii* infection and Zamboni *et al.* showed that TLR2  
229 is involved in TNF and interferon- $\gamma$  (IFN- $\gamma$ ) production (Zamboni *et al.*, 2004).  
230 Myeloid dendritic cells (DCs) can be infected by *C. burnetii* and DCs constitute a  
231 protective niche for the bacteria as organisms replicate within DCs (Shannon *et al.*,  
232 2005). In contrast, avirulent bacteria which are eliminated by the host immune  
233 response stimulate DC maturation and IL-12 production. Phase I bacteria escape  
234 intracellular killing by inhibiting the final phagosome maturation step-cathepsin  
235 fusion (Ghigo *et al.*, 2002). IFN- $\gamma$  restores this fusion step and allows intracellular  
236 killing of *C. burnetii* by recruiting the GTPase Rab7, which is involved in traffic  
237 regulation (Raoult *et al.*, 2005). Moreover IFN- $\gamma$  induces the killing of *C. burnetii*  
238 through the apoptosis of *C. burnetii*-infected macrophages by inducing the expression  
239 of membrane tumour necrosis factor (Raoult *et al.*, 2005).

240 The control of the primary Q fever infection involves systemic cell mediated  
241 immune response and granuloma formation. The granulomatous lesions have a central  
242 open space and a fibrin ring, and are referred to as doughnut granulomas. Immune  
243 control of *C. burnetii* is T-cell dependent but does not lead to *C. burnetii* eradication  
244 (Honstette *et al.*, 2004). *C. burnetii* DNA can also be found in circulating monocytes

245 or bone marrow of people infected months or years earlier (Capo *et al.*, 2003).  
246 Specific immunoglobulins are secreted following infection. IgG is mainly directed  
247 against phase II antigen, whereas IgM is directed against both phase I and II cells  
248 (Maurin and Raoult, 1999).

249 *C. burnetii* infection may become chronic. Once established, chronic Q fever  
250 is characterised by defective cell-mediated immunity, thus emphasizing the major role  
251 of cell-mediated immunity in the protection against *C. burnetii*. Lymphocytes from  
252 patients with Q fever endocarditis do not proliferate in response to *C. burnetii* antigen,  
253 in contrast to lymphocytes from patients with acute Q fever (Koster *et al.*, 1985). The  
254 mechanisms of this specific unresponsiveness may include alterations in T-cell  
255 subsets, but CD4 T-cell lymphopenia was observed in patients with Q fever  
256 endocarditis (Sabatier *et al.*, 1997). Finally, a severe inflammation is found in almost  
257 every patient with Q fever endocarditis as they exhibit up-regulated levels of TNF and  
258 IL-6, two inflammatory cytokines, type II TNF receptors and IL-1 receptor antagonist  
259 (Mege, 2007).

## 260 **Clinical manifestations**

261 The main characteristic of Q fever is its clinical polymorphism, so that  
262 diagnosis can only be made by systematic tests. It is likely that factors such as the  
263 route of infection and the inoculum size, affect the expression of *C. burnetii* infection.  
264 Indeed the respiratory route is associated with pneumonia and the intraperitoneal route  
265 with hepatitis (Marrie *et al.*, 1996). High inocula are associated with myocarditis  
266 (Maurin and Raoult, 1999). Gender and age also affect the expression of *C. burnetii*  
267 infection. Men are symptomatic more often than women despite comparable exposure  
268 and seroprevalence (Tissot-Dupont *et al.*, 1992; Maltezou and Raoult, 2002).  
269 Moreover, the prevalence of clinical cases in children significantly increases with age

270 and symptomatic Q fever occurs more frequently in people over 15 years old  
271 (Maltezou and Raoult, 2002).

## 272 **Acute Q fever**

273 In an epidemiological survey that took place in Marseille between 1985 and  
274 1998, Q fever diagnosis was 1,070 patient with a male/female sex ratio of 2.45  
275 (Raoult *et al.*, 2000). The mean age of acute Q fever patients was  $45.32 \pm 16.56$  years  
276 (range, 6-87 years). There was no statistically significant age difference according to  
277 sex. Occupation was studied for 477 patients and 8% of them were farmers or  
278 veterinarians, a rural existence was noted for 162 (37.9%), ingestion of farm goat  
279 cheese was noted for 85/366 (23.2%), and contact with newborn or pregnant animals  
280 for 142/401 (35.4%). Immunosuppression was noted for 20 patients (4.7%) (Raoult *et*  
281 *al.*, 2000).

282 The incubation period has been estimated to be approximately 20 days (range,  
283 14 to 39 days). There is no typical form of acute Q fever and the clinical signs vary  
284 greatly from patient to patient. The most frequent clinical manifestation of acute Q  
285 fever is probably a self-limited febrile illness (91%) which is associated with severe  
286 headaches (51%), myalgias (37%), arthralgias (27%) and cough (34%) (Tissot-  
287 Dupont and Raoult, 2007). The main symptoms fever, pulmonary signs, and elevated  
288 liver enzyme levels can coexist. Of 323 hospitalized patients with acute Q fever in  
289 France, 25% presented with the three symptoms, 40% presented with fever and  
290 elevated liver enzyme levels, 17% presented with fever and pulmonary signs, and 4%  
291 presented with only fever, pulmonary signs, or elevated liver enzyme levels (Tissot-  
292 Dupont *et al.*, 1992). Atypical pneumonia is also a major clinical presentation and  
293 abnormal chest X rays can be found in 27% of the patients (Tissot-Dupont and Raoult,  
294 2007). After primary infection, 60% of the patients will exhibit a symptomatic

295 seroconversion, and only 4% of the symptomatic patients will be admitted to  
296 hospitals. A chronic disease will develop in at-risk patients.

297 **Prolonged fever.** Prolonged fever is usually accompanied by severe headaches. The  
298 fever may reach from 39 to 40°C, usually remaining elevated all day. Fever typically  
299 increases to a plateau within 2 to 4 days, and then after 5 to 14 days the temperature  
300 returns rapidly to normal. However, in untreated patients, fever may last from 5 to 57  
301 days (Derrick, 1973). The duration of fever is longer in elderly patients (Derrick,  
302 1973).

303 **Pneumonia.** Atypical pneumonia is one of the most commonly recognized forms of  
304 acute Q fever. Most cases are clinically asymptomatic or mild, characterized by a  
305 nonproductive cough, fever, and minimal auscultatory abnormalities, but some  
306 patients present with acute respiratory distress (Raoult *et al.*, 1990b). Pleural effusion  
307 can also be present. Findings on the chest radiograph are nonspecific. The duration of  
308 symptoms varies from 10 to 90 days. The mortality rate ranges from 0.5 to 1.5%,  
309 depending upon the series (Tissot-Dupont *et al.*, 1992). Pneumonia is the major  
310 manifestation of acute Q fever in Nova Scotia, Canada, in the Basque country in  
311 Spain, and in Switzerland, while in France, Ontario, California, and Australia,  
312 hepatitis is the predominant form of acute Q fever (Fournier *et al.*, 1998).

313 **Hepatitis.** Three major forms of hepatitis may be encountered: an infectious hepatitis-  
314 like form of hepatitis with hepatomegaly but seldom with jaundice, clinically  
315 asymptomatic hepatitis, and prolonged fever of unknown origin with characteristic  
316 granulomas on liver biopsy. Hepatitis is the most common presentation worldwide,  
317 particularly in France and Australia. Alkaline phosphatase, AST, and ALT levels are  
318 usually mildly elevated to two to three times the normal level (Marrie, 1988). Q fever  
319 hepatitis is usually accompanied clinically by fever and less frequently by abdominal

320 pain (especially in the right hypochondrium), anorexia, nausea, vomiting, and  
321 diarrhea. Progressive jaundice and palpation of a mass in the right hypochondrium  
322 have also been reported. Frequently, patients with hepatitis exhibit autoantibodies,  
323 including antibodies directed to smooth muscle, anticardiolipin antibodies,  
324 antiphospholipid antibodies, circulating anticoagulant, and antinuclear antibodies  
325 (Tissot-Dupont and Raoult, 2007).

326 **Cardiac involvement.** Cardiac involvement is found in 2% of the acute Q fever cases  
327 and myocarditis is the leading cause of death (Fournier *et al.*, 2001). The  
328 pathophysiology of the heart damage is still not clear, although a relationship has been  
329 demonstrated between the onset of a myocarditis and the inoculum size in an  
330 experimental model (La Scola *et al.*, 1997). Myocarditis may be associated with  
331 pericarditis, and a pericardial effusion may be observed on chest radiographs. Clinical  
332 manifestations of Q fever pericarditis are not specific and most often correspond to a  
333 fever with thoracic pain. However, *C. burnetii* is the main cause of pericarditis in  
334 southern France and a frequent one in Spain and in the United Kingdom (Tissot-  
335 Dupont and Raoult, 2007).

336 **Skin rash.** Skin lesions have been found in 5 to 21% of Q fever patients in different  
337 series. The Q fever rash is nonspecific and may correspond to pink macular lesions or  
338 purpuric red papules of the trunk (Maurin and Raoult, 1999).

339 **Neurologic signs.** There are 3 major neurological entities associated with Q fever: (1)  
340 meningoencephalitis or encephalitis; (2) lymphocytic meningitis and (3) peripheral  
341 neuropathy (Bernit *et al.*, 2002). Patients with central nervous system involvement do  
342 not demonstrate differences in predisposing conditions, but more frequently have  
343 occupational exposure to goats than patients with acute Q fever but no neurological  
344 involvement (Bernit *et al.*, 2002).



345 **Chronic Q fever**

346 Chronic Q fever may develop many months to years after initial infection,  
347 manifesting as bacterial culture-negative endocarditis in up to 75% of cases (Gami *et*  
348 *al.*, 2004). Chronic Q fever occurs almost exclusively in patients with predisposing  
349 conditions, including those with heart valve lesions, vascular abnormalities, and  
350 immunosuppression (Fenollar *et al.*, 2001). Figure 1 shows the natural history of Q  
351 fever in the absence of treatment.

352 **Endocarditis.** The most frequent and studied preservation of chronic Q fever is  
353 endocarditis (Figure 1). More than 800 cases were reported in various studies between  
354 1949 and 2005 (Tissot-Dupont and Raoult, 2007). The main series were studied in the  
355 United Kingdom and in Ireland (227 cases), in France (264 cases), in Spain (62  
356 cases), in Israel (35 cases), in Switzerland (21 cases), in Australia (18 cases) and in  
357 Canada (10 cases). Q fever endocarditis is often a severe disease associated with a  
358 long diagnostic delay. Q fever represents 5% of endocarditis cases in France (Brouqui  
359 and Raoult, 2006). It occurs almost exclusively in patients with a previous cardiac  
360 defect or in immunocompromised patients. The aortic and mitral valves are mostly  
361 involved. Q fever prosthetic valve endocarditis has been increasingly reported over  
362 recent years (Maurin and Raoult, 1999). The male/female ratio is 75%, and most  
363 patients are older than 40 years. The clinical presentation has changed over the last 30  
364 years. With faster diagnoses, the prevalence of heart failure, hepatomegaly,  
365 inflammatory syndrome, anaemia and leucopenia and abnormal liver function tests  
366 have decreased significantly (Houpikian *et al.*, 2002).

367 The prognosis of chronic Q fever was dramatically improved over the course  
368 of just a few years. The mortality rate was 37% in a series of 79 patients reported in  
369 1987 (Raoult *et al.*, 1987), whereas it was only 15% in more recent series of 116

370 patients, between 1997 and 2000 (Tissot-Dupont and Raoult, 2007). Among the most  
371 recently diagnosed patients the death rate was under 5% (Raoult *et al.*, 1999) an  
372 improvement that is probably related to the earlier diagnosis, the efficient treatment  
373 and the better follow up (Siegman-Igra *et al.*, 1997).

#### 374 **Other clinical manifestations of Chronic Q fever**

375       Vascular infection is the second most frequent presentation of Q fever. An  
376 aortic aneurism can be infected by *C. burnetii*, leading to an intestinal fistula or a  
377 spondylitis, as well as a vascular graft. The prognosis is poor in the absence of  
378 treatment (Botelho-Nevers *et al.*, 2007).

379       Other manifestations of chronic Q fever are osteoarticular infections, including  
380 osteomyelitis, osteoarthritis, and aortic graft infection with contiguous spinal  
381 osteomyelitis (Maurin and Raoult, 1999), chronic hepatitis in alcohol addicts (Raoult  
382 *et al.*, 2000), pseudotumors of the spleen, of the lung (Lipton *et al.*, 1987), infection of  
383 a ventriculo-peritoneal drain (Lohuis *et al.*, 1994). Chronic fatigue syndrome has also  
384 been reported infrequently as a possible clinical manifestation following acute Q  
385 fever. The latter may be associated with cytokine dysregulation and presents as  
386 fatigue, myalgia, arthralgia, night sweats, mood changes and sleep disturbance.

#### 387 **Pregnant Women**

388       When a woman is infected by *C. burnetii* during pregnancy, the bacteria settle  
389 in the uterus and in the mammary glands. The consequences are of great importance:  
390 a) there is an immediate risk for the mother; b) there is an immediate risk for the fetus  
391 as 100% of the fetuses abort when the infection occurs during the first trimester and  
392 there is a risk of preterm delivery, or low birth-weight if infection occurs during the  
393 second or third trimester; c) there is a long-term risk of chronic Q fever in the mother.

394 Few data are available on the consequences of Q fever during pregnancy. To date,  
395 only 38 cases have been published, demonstrating that Q fever in pregnant women is  
396 associated with high morbidity and mortality (Carcopino *et al.*, 2007). Thus, Q fever  
397 during pregnancy can result in spontaneous abortion (26%), intrauterine fetal death  
398 (5.3%), premature delivery (44.7%), or intrauterine growth retardation (5.3%)  
399 (Carcopino *et al.*, 2007). Normal obstetric outcome is possible (15.8%).  
400 Transplacental infection of the fetus in utero is possible, but its consequences are still  
401 unknown, and its association with obstetric complications remains hypothetical  
402 (Carcopino *et al.*, 2007). In a work of our laboratory it was shown that Q fever, when  
403 contracted during pregnancy, can result in abortions or neonatal deaths (9 cases,  
404 38%), premature births, low birth weight (8 cases, 33%), or no abnormalities (7 cases,  
405 29%) (Raoult *et al.*, 2002). Q fever during pregnancy also has important consequences  
406 for the mother, with higher risk of chronic form and spontaneous abortions of future  
407 pregnancies. Although most infected pregnant women present with fever, flu-like  
408 illness, severe thrombocytopenia, and atypical pneumonia have also been reported  
409 (Maurin and Raoult, 1999). However, Q fever in pregnant women may also be  
410 asymptomatic (Marrie, 1993). Serological profiles at the time of diagnosis were  
411 suggestive of acute Q fever in 14 (58.3%) of 24 pregnant women for whom serology  
412 was performed and of chronic Q fever in 10 (41.7%) (Maurin and Raoult, 1999).

### 413 **Clinical manifestations in animals**

414 In contrast to acute human Q fever animal infection with *C. burnetii* is, in  
415 most cases, so strikingly asymptomatic that the term coxiellosis is considered a more  
416 appropriate designation than animal Q fever (Lang, 1988). In animals, during the  
417 acute phase, *C. burnetii* can be found in the blood, lungs, spleen, and liver whereas  
418 during the chronic phase it is presented as a persistent shedding of *C. burnetii* in feces

419 and urine. Most animals remain totally asymptomatic, including a lack of fever.  
420 However, low birth weight animals can occur (Marrie *et al.*, 1996). Aborted fetuses  
421 usually appear normal and the abortion rates can range from 3 to 80% (Marrie, 2007).  
422 Infected placentas exhibit exudates and intracotyledonary fibrous thickening. A severe  
423 inflammatory reponse is noted in the myometrium of goats and metris is frequently a  
424 unique manifestation of the disease in cattle (Arricau-Bouvery and Rodolakis, 2005).  
425 *C. burnetii* can also be recovered from milk for up to 32 months. Goat shed *C.*  
426 *burnetii* in feces before and after kidding and the mean duration of excretion is 20  
427 days.

#### 428 **Diagnosis**

429 **Collection and storage of specimens.** *C. burnetii* virulence is particularly high and  
430 only biosafety level 3 laboratories and experienced personnel should be allowed to  
431 manipulate contaminated specimens and cultivate this microorganism from clinical  
432 samples. Several human specimens are suitable for the detection of *C. burnetii*, but  
433 their availability depends on the clinical presentation. All specimens, excluding whole  
434 blood which should be kept at 4°C, should be stored at -80°C and should be  
435 forwarded on dry ice to the diagnostic laboratory (Fournier *et al.*, 1998).

436 **Culture.** *C. burnetii* isolation from biological samples is carried out on HEL cells  
437 using the Shell Vial centrifugation technique (Marrero and Raoult, 1989). Cell  
438 monolayers in shell vials are inoculated with 1 ml of clinical specimen and  
439 centrifuged (700 x g at 20°C) for 1 h to enhance attachment and penetration of *C.*  
440 *burnetii* into cells. Inoculated monolayers are incubated at 37°C in 5% CO<sub>2</sub> for 5 to 7  
441 days. *C. burnetii* is usually observed by microscopic examination of cell monolayers  
442 after Gimenez or immunofluorescence staining

443 **Immunodetection.** The detection of *C. burnetii* in tissues is especially informative in  
444 patients who are undergoing treatment for chronic Q fever. Samples can be tested  
445 fresh or after formalin fixation and paraffin embedding. Immunodetection is carried  
446 out using immunoperoxidase techniques or immunofluorescence with polyclonal or  
447 monoclonal antibodies (Maurin and Raoult, 1999). Only this last technique can be  
448 used on paraffin-embedded samples (Raoult *et al.*, 1994). Recently, Lepidi *et al.*  
449 proposed a new method named autoimmunohistochemistry for the detection of the *C.*  
450 *burnetii* endocarditis (Lepidi *et al.*, 2006).

451 **Molecular biology.** During the last years, several PCR based diagnostic assays were  
452 developed to detect *C. burnetii* DNA in cell cultures and in clinical samples. These  
453 assays used conventional PCR, nested PCR or real-time PCR conditions with  
454 LightCycler, SYBR Green or TaqMan chemistry (Klee *et al.*, 2006). The Light-  
455 Cycler Nested PCR (LCN-PCR), a rapid nested-PCR assay that uses serum as a  
456 specimen and the LightCycler as a thermal cycler, targeting a multicopy 20-copy  
457 htpAB-associated element sequence has been adapted for the diagnosis of both acute  
458 and chronic Q fever (Fenollar and Raoult, 2007). The LCN-PCR assay may be helpful  
459 in establishing an early diagnosis of chronic Q fever (Fenollar *et al.*, 2004). Due to its  
460 high sensitivity and specificity, the repetitive element, IS 11-11, is the best target gene  
461 for the detection of *C. burnetii* in patients with active Q fever (Fenollar and Raoult,  
462 2004). Recently, the complete sequences of the genome of *C. burnetii* became  
463 available, allowing a large choice of DNA targets.

464 **Serology.** Since the clinical diagnosis is difficult, in most instances, the diagnosis of  
465 Q fever relies upon serology. A variety of serological techniques are available, but the  
466 indirect microimmunofluorescent antibody test has become the reference technique.  
467 Immunoglobulin M antibodies reactive with phase II *C. burnetii* appear rapidly, reach

468 high titers within 14 days and persist for 10 to 12 weeks (Maurin and Raoult, 1999).  
469 Immunoglobulin M antibodies reactive with phase I antigens are usually at a much  
470 lower titer during acute infection. Immunoglobulin G antibodies reactive with phase II  
471 antigens reach peak titers about 8 weeks after the onset of symptoms, while those  
472 reactive with phase I antigens develop only very slowly and remain at lower titers  
473 than antibodies to phase II antigens, even after a year. In chronic Q fever, where there  
474 is persistence of organisms, the IgG titers to phase I and phase II antigens may both be  
475 high, and the presence of IgA antibody to phase I antigen is usually, although not  
476 exclusively, associated with chronic infection. Seroconversion or a fourfold increase  
477 in titer indicates acute infection. Elevated levels of IgG ( $>1/200$ ) and IgM ( $>1/25$ ) to  
478 phase II antigens also indicate a recent infection. High titers of IgG ( $1/800$ ) and/or  
479 IgA ( $>1/50$ ) to phase I antigen are found in chronic infections. Serology should be  
480 used to follow-up patients with acute Q fever to determine if treatment was successful  
481 and to enable the early diagnosis of chronic infections (Landais *et al.*, 2007).

482 **Diagnosis in animals.** Isolation of *C. burnetii* is not performed for routine diagnosis  
483 in veterinary medicine. Routine diagnosis of Q fever in animals is usually established  
484 by examination of fixed impressions or smears prepared from the placenta stained by  
485 the Stamp, Gimenez or Machiavello methods, associated with serological tests. The  
486 CF test, which is the OIE prescribed serological test, is weakly sensitive and the  
487 antigen used in this test frequently fails to detect antibodies in sheep or goats  
488 (Kovacova *et al.*, 1998). The ELISA test is more sensitive than the CF test but it does  
489 not allow individual identification of animals that shed *C. burnetii* in faeces or milk.  
490 PCR kits are becoming available and provide a specific, sensitive and rapid tool for  
491 the detection of *C. burnetii* in various clinical samples (Berri *et al.*, 2003).

492 **Antimicrobial Susceptibility Testing**

493 Antibiotic susceptibility testing of *C. burnetii* is difficult because this  
494 organism is an obligate intracellular bacterium. Three models of infection have been  
495 developed: animals, chick embryos and cell culture. The current method used to test  
496 the antibiotic susceptibility of *C. burnetii* is based on cell culture models (Rolain,  
497 2007).

498 A number of cell lines have been used to test antibiotic activity against  
499 intracellular *C. burnetii*, including murine macrophage-like cell lines (P388D1 and  
500 J774) and a murine fibroblast cell line (L929) (Akporiaye *et al.*, 1983; Baca *et al.*,  
501 1981; Baca *et al.*, 1985; Burton *et al.*, 1978; Roman *et al.*, 1986). Yeaman *et al.*  
502 described an acute *C. burnetii* infection model in acutely infected L929 cells (Yeaman  
503 *et al.*, 1989). Bacteriostatic activity was demonstrated against *C. burnetii* Nine Mile  
504 and Priscilla isolates with doxycycline (10 mg/ml), rifampin (1 mg/ml), and ofloxacin  
505 (5 mg/ml). Moreover, they used chronically infected L929 cells to test the bactericidal  
506 activity of antibiotics against *C. burnetii* (Yeaman *et al.*, 1987). They found that the  
507 percentage of infected cells was not reduced by tetracycline, erythromycin, or  
508 sulfamethoxazole at concentrations up to 10 mg/ml and was only slightly reduced by  
509 chloramphenicol, doxycycline, and trimethoprim, suggesting that these drugs were not  
510 bactericidal. In contrast, the quinolone compounds and rifampin reduced the  
511 percentage of infected cells from 100% to 2, 2, 7, and 4%, respectively, after 10 days  
512 of continuous culture treatment. Torres and Raoult have developed a Shell-Vial assay  
513 with human embryonic lung cells (HEL) for assessment of the bacteriostatic effect of  
514 antibiotics (Torres and Raoult, 1993). By this technique, amikacin and amoxicillin  
515 were not effective against *C. burnetii*, ceftriaxone and fucidic acid were inconsistently  
516 active (Torres and Raoult, 1993), whereas cotrimoxazole, rifampin, doxycycline,  
517 clarithromycin and quinolones were bacteriostatic (Rolain *et al.*, 2005b; Maurin and

518 Raoult, 1993). Raoult *et al.*, using P288D1 and L929 cells, showed that pefloxacin,  
519 rifampin and doxycycline (Raoult *et al.*, 1990a) as well as clarithromycin were  
520 bacteriostatic against *C. burnetii* (Maurin and Raoult, 1993). Moreover, Maurin *et al.*  
521 demonstrated that the addition of a lysosomotropic alkalinizing agent, chloroquine, to  
522 antibiotics improved the activities of doxycycline and pefloxacin which then became  
523 bactericidal (Maurin *et al.*, 1992). That result has been corroborated by the  
524 demonstration of *in vivo* efficacy for the combination of doxycycline and  
525 hydroxychloroquine (Raoult *et al.*, 1999).

526 High level resistance to fluoroquinolones due to an amino acid substitution of  
527 Gly instead of Glu at position 87 of the GyrA has been reported (Musso *et al.*, 1996).  
528 Porins have been demonstrated in *C. burnetii* cells, but their potential role in antibiotic  
529 resistance associated with impermeability remains undefined (Banerjee-Bhatnagar *et*  
530 *al.*, 1996). Moreover, *C. burnetii* strains have been found to present differences in  
531 susceptibility to erythromycin (Raoult *et al.*, 1991) and in susceptibility to  
532 doxycycline, ciprofloxacin, and rifampin (Yeaman and Baca, 1990). *In vitro* selection  
533 of *C. burnetii* strains resistant to tetracyclines has been also performed (Brezina *et al.*,  
534 1975).

535 The real-time quantitative PCR (RT-PCR) assay has also been used for the  
536 determination of the antibiotic susceptibility of *C. burnetii* (Boulos *et al.*,  
537 2004; Brennan and Samuel, 2003). RT-PCR confirmed that MICs against doxycycline,  
538 fluoroquinolone compounds and rifampicin were in the range 1 to 4 mg/L and that  
539 telithromycin was the most effective macrolide compound (Boulos *et al.*, 2004). By  
540 the use of this assay, for the first time a human isolate of *C. burnetii* resistant to  
541 doxycycline was found in a patient with Q fever endocarditis (Rolain *et al.*, 2005a).

## 542 **Treatment**



543 The guideline recommendations for the treatment of Q fever are summarised in Table  
544 2.

545 **Treatment of Acute Q fever.** The recommended regimen for acute Q fever associates  
546 doxycycline (200 mg daily for 14 days) to hydroxychloroquine, which alkalinizes the  
547 phagolysosomes (Maurin and Raoult, 1999) . Fluoroquinolones are considered to be a  
548 reliable alternative and have been advocated for patients with Q fever  
549 meningoencephalitis, because they penetrate the cerebrospinal fluid (Maurin and  
550 Raoult, 1999). Cotrimoxazole and rifampin can be used in case of allergy to  
551 tetracyclines or contraindication (Tissot-Dupont and Raoult, 2007). Erythromycin and  
552 other new macrolides such as clarithromycin and roxithromycin, could be considered  
553 a reasonable treatment for acute *C. burnetii* infection (Gikas *et al.*, 2001).

554 **Acute Q fever in children.** In children younger than 8 years, co-trimoxazole has been  
555 recommended, because of the adverse effects of tetracyclines and quinolones in this  
556 age group. However, it has now been admitted that age is not a contraindication to  
557 doxycycline, when the antibiotic is specific of the disease (Tissot-Dupont and Raoult,  
558 2007). Moreover, in patients with prolonged fever, the addition of corticosteroids to  
559 treatment might prove beneficial and interferon  $\gamma$  was successfully administered to a  
560 3-year-old child with a prolonged fever unresponsive to appropriate treatment against  
561 *C. burnetii* (Maltezou and Raoult, 2002).

562 **Acute Q fever during pregnancy.** Specific treatment using cotrimoxazole (800/160)  
563 BID, until delivery, associated to folinic acid (25 mg OD) is recommended (Raoult *et*  
564 *al.*, 2002). Recently, Carcopino *et al.* compared the incidence of obstetric and  
565 maternal Q fever complications for women who received long-term cotrimoxazole  
566 treatment with that for women who did not receive long-term cotrimoxazole treatment  
567 (Carcopino *et al.*, 2007). They found that long-term cotrimoxazole treatment protected

568 against maternal chronic Q fever, placental infection, obstetric complications and  
569 especially of intrauterine fetal death. However, obstetric complications were observed  
570 in 81.1% of pregnant women who did not receive long-term cotrimoxazole therapy.  
571 After delivery, if the woman shows a chronic serology profile, she should be treated  
572 as a chronic case, in order to prevent endocarditis and relapsing abortions. Breast  
573 feeding is contraindicated (Raoult *et al.*, 2002)

574 **Chronic Q fever.** Although the optimal duration of therapy is unknown, the current  
575 recommendations for the treatment of chronic Q fever are 100 mg of doxycycline  
576 orally twice daily with 600 mg of hydroxychloroquine by mouth once daily for at  
577 least 18 months. Serologic testing is recommended on a regular basis during therapy,  
578 and the main predictive criterion of clinical cure is a decrease of phase I IgG antibody  
579 titers to <200 (Karakousis *et al.*, 2006). In general, the antibody titers decrease slowly  
580 with treatment (Raoult *et al.*, 1999). However, the kinetics of antibody titer decrease  
581 in patients treated with doxycycline may vary, suggesting that some patients should be  
582 treated for >18 months to be cured (Rolain *et al.*, 2003). Successful evolution is  
583 evaluated by the decrease of antibody titers (IgG and IgA) to phase I that should reach  
584 two dilutions in one year at the minimum. When available, the *C. burnetii* strain  
585 should be cultured from blood or valves in order to evaluate the doxycycline MIC: the  
586 doxycycline plasmatic level should be adjusted between 1.5 and 2 MICs (Rolain *et*  
587 *al.*, 2005a). Hydroxychloroquine dosing should be adapted according to plasmatic  
588 levels ( $1\pm 0.2$  mg/L). Recently, Rolain *et al.* found isolates of *C. burnetii* resistant to  
589 doxycycline (MIC:8 $\mu$ g/mL) from patients with Q fever endocarditis (Rolain *et al.*,  
590 2005a; Rolain *et al.*, 2005b)

591 **Q fever in patients at risk of chronic evolution.** Acute Q fever in any patient  
592 presents a risk factor for chronic evolution (vascular damage, vascular or valvular

593 graft, aneurism) and should be treated according to the same protocol as chronic cases  
594 (Fenollar *et al.*, 2001). Patients with acute Q fever should be systematically tested -  
595 including those patients who do not have known underlying factors- 3 and 6 months  
596 after the onset of disease (Landais *et al.*, 2007). Those with phase I IgG antibody titers  
597  $\geq 1: 800$  should be investigated for possible infective endocarditis using  
598 transesophageal echocardiography and PCR to allow for early detection of the disease

### 599 **Treatment in ruminants**

600 In ruminants, antibiotic treatment generally consist in administering two  
601 injections of oxytetracycline (20 mg per kg bodyweight) during the last month of  
602 gestation, although this treatment does not totally suppress the abortions and the  
603 shedding of *C. burnetii* at lambing (Berri *et al.*, 2007). In known infected herds,  
604 segregating pregnant animals indoors, burning or burying reproductive offal, or  
605 administering tetracycline (8 mg/kg/day) prophylactically in the water supply prior to  
606 parturition may reduce spread of the organism.

### 607 **Prevention**

608 Epidemiological studies indicate Q fever as a public health problem in many  
609 countries, including France, the United Kingdom, Italy, Spain, Germany, Israel,  
610 Greece, and Canada (Nova Scotia). In Germany, 7.8% of 21,191 tested cattle, 1.3% of  
611 1,346 tested sheep, and 2.5% of 278 tested goats had evidence of *C. burnetii* infection  
612 (Hellenbrand *et al.*, 2001). In Cyprus, the prevalence of IgG antibodies against *C.*  
613 *burnetii* phase II antigen was estimated at 48.2% for goats, 18.9% for sheep, and 24%  
614 for bovines (Psaroulaki *et al.*, 2006). In Iran goats had a significantly higher average  
615 seroprevalence (65.78%) than cattle (10.75%) (Khalili and Sakhaee, 2009). In  
616 Zimbabwe, serological evidence of Q fever infection was found in 39% of cattle, and  
617 in 10% of goats (Kelly *et al.*, 1993). In the USA goats had a significantly higher

618 average seroprevalence (41.6%) than sheep (16.5%) or cattle (3.4%) (McQuiston and  
619 Childs, 2002). Q fever remains primarily an occupational hazard in persons in contact  
620 with domestic animals such as cattle, sheep and, less frequently, goats. Persons at risk  
621 from Q fever include farmers, veterinarians, abattoir workers, those in contact with  
622 dairy products, and laboratory personnel performing *C. burnetii* culture and more  
623 importantly working with *C. burnetii*-infected animals.

624 It is important to mention that during the last years the prevalence of chronic  
625 Q fever in the USA has increased because of the Iraq war. Q fever is apparently  
626 hyper-endemic in Iraq and many US soldiers serving in this area have been exposed to  
627 *C. burnetii* and diagnosed as suffering by Q fever. As Q fever may reveal more than  
628 10 years after primo infection (symptomatic or not and diagnosed or not), it is  
629 possible that the Iraq war veterans will be an important reservoir of potential chronic  
630 Q fever cases that will increase the real prevalence of the disease.

631 In common with all zoonotic diseases, control of the disease in animals will  
632 influence the level of disease seen in man. Appropriate tick control strategies and  
633 good hygiene practice can decrease environmental contamination. Infected fetal fluids  
634 and membranes, aborted fetuses and contaminated bedding should be incinerated or  
635 buried. In addition, manure must be treated with lime or calcium cyanide 0.4% before  
636 spreading on fields; this must be done in the absence of wind to avoid spreading of the  
637 microorganism faraway. Antibiotic treatment may be performed to reduce the number  
638 of abortions and the quantity of *C. burnetii* shed at parturition. Although it is very  
639 expensive, infected animals should be removed from herds or provided with separate  
640 containment facilities in which to give birth. Workers in the animal industry should be  
641 fully informed about the risk factors of acquiring Q fever and laboratories should be  
642 provided with appropriate safety facilities and equipment.

643 Three types of vaccine have been proposed for providing human protection  
644 against Q fever: the attenuated live vaccine (produced and tested in Russia but  
645 subsequently abandoned because of concern about its safety); chloroform– methanol  
646 residue extracted vaccine or other extracted vaccines (tested in animals but not  
647 humans); and the whole-cell formalin-inactivated vaccine (Q-Vax), which is  
648 considered acceptably safe for humans (Chiu and Durrheim, 2007). The only  
649 economic study undertaken in Australia on Q fever vaccine was performed before the  
650 completion of the national vaccination program and assumed a Q-Vax efficacy of  
651 98% (Chiu and Durrheim, 2007). Since Q fever in humans is often an occupational  
652 hazard, vaccination should be considered primarily in exposed populations (Maurin  
653 and Raoult, 1999). Moreover, vaccination should probably also be considered in  
654 persons not professionally exposed but at risk for chronic Q fever, including patients  
655 with cardiac valve defects, vascular aneurysms, or prostheses and  
656 immunocompromised patients.

657 Vaccines can prevent abortion in animals, and it is evident that a phase I vaccine must  
658 be used to control the disease and to reduce environmental contamination and thus,  
659 the risk of transmission to humans. The widespread application of such a vaccine in  
660 cattle in Slovakia in the 1970s and 1980s significantly reduced the occurrence of Q  
661 fever in that country (Kovacova and Kazar, 2002). Reducing exposure to raw milk for  
662 at risk people (pregnant women, patients with cardiac pathology or immunosuppressed)  
663 and promoting the use of pasteurized milk and its products will also contribute to  
664 lowering the prevalence of Q fever.

665

666

667

668 **Conflict of Interest Statement**

669 None.

670

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1001 Table 1. Guidelines for the treatment of Q fever

1002

1003 **Figure legends**

1004 Figure1. Q fever natural history in the absence of treatment

1005 Figure 2. Immunohistochemical detection of *C. burnetii* in a resected cardiac valve

1006 from a patient with a Q fever endocarditis, using a monoclonal antibody and

1007 hematoxylin counterstain. Note the intracellular location of the bacteria in the

1008 macrophage cytoplasm (original magnification x 400).

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Table 1

Clinical feature	Patient cohort	Treatment	Duration	Reference
Acute Q fever	Adults	doxycycline (100 mg/day)	14 days	(Maurin and Raoult, 1999)
		fluoroquinolones (200 mg three times a day or pefloxacin (400 mg)	14 to 21 days	(Maurin and Raoult, 1999)
		rifampin (1,200 mg/day)	21 days	(Raoult, 1993)
	Pregnant	trimethoprim (320 mg) and sulfamethoxazole (1600 mg )	>5 weeks	(Carcopino <i>et al.</i> , 2007)
Chronic Q fever	Children	doxycycline (100 mg/day)	10-14 days	(Maurin and Raoult, 1999)
	Adults	doxycycline (100 mg/day) and hydroxychloroquine (600mg)	>18 months	(Carcopino <i>et al.</i> , 2007)

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children

trimethoprim and sulfamethoxazole

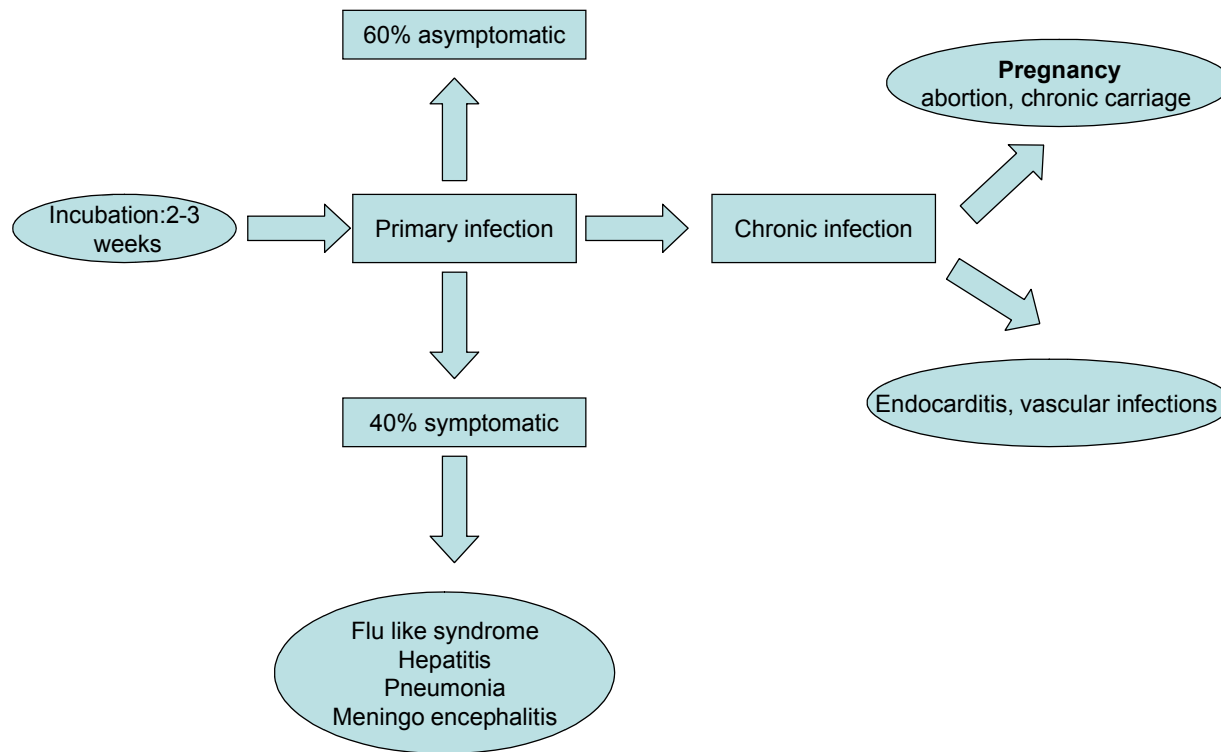
>18 months

(Nourse *et al.*, 2004)

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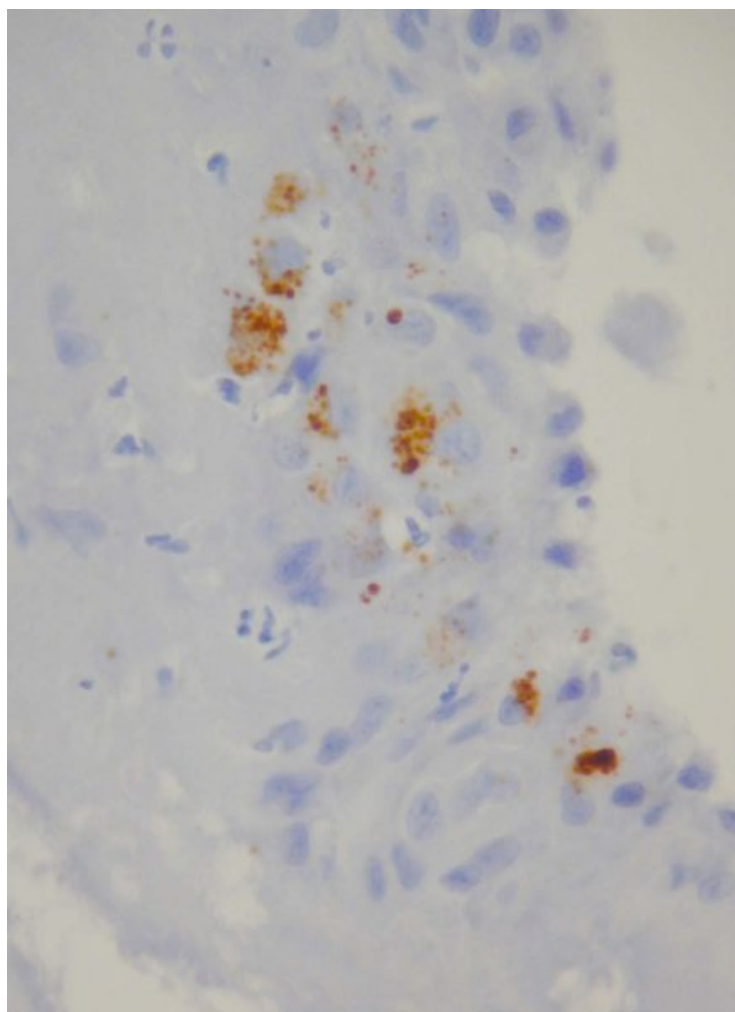
1 Figure1.



2

3 Figure2.

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