Q Fever: A Re-Emerging Disease?

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Abstract

Q fever is a mainly airborne zoonosis with public health concern throughout the world caused by the highly contagious, obligate intracellular bacteria Coxiella burnetii. It is an important occupational zoonosis since its discovery in 1935; it has been shown to infect a wide range of hosts, including humans. Although Q fever is a disease closely related to occupations such as handling livestock, most of the previous studies concerned with general population. A recent outbreak in Europe reminds us that this is still a significant pathogen of concern, very transmissible with a very low infectious dose. For these reasons it has also featured regularly on various threat lists, as it may be considered to be used as a bio-weapon. Therefore, we reviewed the literatures on Q fever to highlight the epidemiologic, economic and public health impact of Q fever as a basis for designing effective control strategies.

Keywords: Q fever; Epidemiology; Public health hazards

Introduction

Q fever is an important occupational zoonotic disease caused by the obligate intracellular bacterium Coxiella burnetii and has great public health significance worldwide [1]. The disease first described in 1937 in Queensland by E.H. Derrick in association with the meat and livestock industry [2]. Q fever is a mainly airborne zoonosis, infection in domestic animals is usually chronic and dormant; the infected pregnant animals excrete the organism into the environment in birth fluids, placenta, fetal membranes, urine and faeces [3]. The most commonly identified sources of human infection are farm animals, especially cattle, goats and sheep, which constitute the best known reservoirs of C. burnetii [3]. Based on epidemiological evidences, the main route of infection in humans is inhalation of contaminated aerosol or dust containing bacteria shed by infected animals. Oral transmission is also discussed and the consumption of contaminated raw milk and dairy-products represents a potential source of human infection [4,5]. The epidemiology and the exact modes of transmission of Q fever remains to be elucidated. Therefore, further research is necessary to improve knowledge of the disease itself. We reviewed the literatures to highlight the epidemiologic, economic and public health impact of Q fever as a basis for designing effective control strategies.

History

The term “Q fever” (for query fever) was proposed in 1937 by Edward Holbrook Derrick to describe febrile illnesses in abattoir workers in Brisbane, Queensland, Australia. In 1935, a disease of unknown origin was first observed in slaughterhouse workers. Patients presented with fever, headache, and malaise. Serologic tests for a wide range of hosts, including humans. Although Q fever is a disease closely related to occupations such as handling livestock most of the previous studies concerned with general population. A recent outbreak in Europe reminds us that this is still a significant pathogen of concern, very transmissible with a very low infectious dose. For these reasons it has also featured regularly on various threat lists, as it may be considered to be used as a bio-weapon. Therefore, we reviewed the literatures on Q fever to highlight the epidemiologic, economic and public health impact of Q fever as a basis for designing effective control strategies.

Etiological Agent

Q fever results from infection by C. burnetii. This organism is an obligate intracellular pathogen, it can be grown only in embryonated eggs or cell cultures or, when necessary, in inoculated laboratory animals. It is a small pleomorphic rod (0.2–0.4 mm wide, 0.4–1.0 mm long) with a membrane similar to that of a Gram-negative bacterium [8]. It has been traditionally placed in the family Rickettsiaceae; however, recent phylogenetic studies have demonstrated that C. burnetii is more closely related to Legionella, Franciscia and Rickettsiella. This organism is now classified in the family Coxiellaceae and order Legionellales in the gamma subdivision of Proteobacteria [9]. Unlike rickettsiae, C. burnetii produces a small, dense, highly resistant spore-like form that is highly stable in the environment [10]. This ability has been attributed to the existence of C. burnetii developmental cycle variants: large-cell variants (LCV), small-cell variants (SCV), and small dense cells (SDC) [11]. The SDC and SCV represent the forms of the bacteria likely to survive extracellularly as infectious particles, as well as its capability to survive relatively extreme environmental conditions. The SCV is resistant to heat, pressure, and chemical agents [12]. The large cell variants (LCVs) are probably the metabolically active cells of this organism. It undergoes sporogenetic differentiation to produce resistant, spore-like forms, the small-cell variants. These are released when the cells lyse and can survive for long periods in the environment [13]. This organism also has two distinct antigenic phases, phase I and phase II. Phase I and II cells are morphologically identical, but differ in some biochemical characteristics including their lipopolysaccharide (LPS) composition. Organisms isolated from infected animals or humans express phase I antigens and are highly infectious. Organisms expressing phase II antigens are less infectious and are recovered after the bacteria are passed repeatedly in cell cultures or eggs. Experimentally infected animals first produce antibodies to phase II antigens and later produce antibodies to phase I antigens. A similar response occurs in humans.

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and is used to distinguish acute from chronic infection [14]. It has the capability to survive permanently inside the macrophages, causing a chronic disease after an acute episode.

**Epidemiology**

Q fever has been described worldwide. Two characteristics of the organism are important in the epidemiology of the disease. These are its ability to withstand harsh environmental conditions, probably as a result of spore formation [10], and its extraordinary virulence for man. A single organism can cause disease in man [15]. *C. burnetii* has been a very successful pathogen. By 1955, Q fever had been reported from 51 countries on five continents [16]. From 1999 to 2004, there were 12 described outbreaks of Q fever from 12 different countries [17]. Q fever considered as a public health problem in many countries, including France, the United Kingdom, Italy, Spain, Germany, Israel, Greece, and Canada (Nova Scotia). In France the incidence of acute Q fever is estimated at 50 per 100,000 inhabitants per year, and that of Q fever endocarditis is estimated at 1 per 106 inhabitants per year [18]. From 1975 to 1995, 67 to 169 Q fever cases were reported annually in United Kingdom to the Communicable Disease Surveillance Center by laboratories in England and Wales [19]. This represents a stable incidence ranging from 0.15 to 0.35 cases per 100,000 population per year. Q fever is endemic in Israel between 1981 and 1990, 758 Q fever cases were reported to the Ministry of Health [20]. A series of 34 patients with Q fever endocarditis was reported more recently [21]. In Germany it is considered as a notifiable disease, 27 to 100 cases are reported annually [22]. In May 1996, a Q fever outbreak occurred in Rollshausen and five surrounding towns in the district of Lohra [22,23]. In this rural area, two flocks of sheep (1,000 to 2,000 and 20 animals, respectively) had been kept near Rollshausen before the Q fever outbreak. Lambing occurred in December 1995 and January 1996. 7.8% out of 21,191 tested cattle, 1.3% of 1346 tested sheep, and 2.5% of 278 tested goats had evidence of *C. burnetii* infection [24]. The largest previously described outbreak occurred in 2003, associated with a farmers’ market in Soest [25]. Infected sheep have been implicated as the source of infection in 24 out of 40 documented outbreaks reported in Germany between 1947 and 1999 [24]. In Cyprus, the prevalence of IgG antibodies against *C. burnetii* phase II antigen was estimated at 48.2% for goats, 18.9% for sheep, and 24% for bovines [26]. In Iran, goats had a significantly higher average seroprevalence (65.78%) than cattle (10.75%) [27]. In Zimbabwe, serological evidence of Q fever infection was found in 39% of goats and 24% for bovines [26]. In Iran, goats had a significantly higher average seroprevalence (65.78%) than cattle (10.75%) [27]. In Zimbabwe, serological evidence of Q fever infection was found in 39% of goats and 24% for bovines [26]. In Iran, goats had a significantly higher average seroprevalence (65.78%) than cattle (10.75%) [27]. In Zimbabwe, serological evidence of Q fever infection was found in 39% of goats and 24% for bovines [26]. Over 40 tick species can be naturally infected [4]. They are likely to play a significant role in transmission among wild vertebrates, but are not considered to be essential in the cycle of *C. burnetii* infection in livestock [33]. However, the organism multiply in the gut cells of ticks and large numbers of *C. burnetii* are shed in tick feces [13]. Contaminated hides and wool may be a source of infection for people either by direct contact or after the faeces have dried and been inhaled as airborne dust particles. Heavy concentrations of microorganisms are secreted in milk, urine, feces, and especially in parturient products of infected pregnant animals. Because of the stability of this agent, dried, infectious particles in barnyards, pastures, and stalls can be a source of infection for periods of up to 150 days [34]. During chronic infection, *C. burnetii* is mainly found in the uterus and mammary glands [33]. Shedding of *C. burnetii* into the environment mainly occurs during parturition; over 109 bacteria are released at the time of delivery [33]. Goats and cows mostly shed *C. burnetii* in milk and vaginal mucus [35,36] whereas oovines shed mostly in faeces [35]. Goats and cows shed *C. burnetii* in milk for several months or years [37].

The aerosol route (inhalation of infected fomites) is the primary mode of human contamination with *C. burnetii* [38]. Ingestion (mainly drinking raw milk) is probably a minor factor in the transmission of *C. burnetii* [39] and is now a point of controversy concerning the possibility of infection by oral route [40]. Further research is required to clarify the probability of infection by oral route. If infection by oral route is proven to be efficient, the sufficient number of pathogens capable of causing Q fever should be determined [41].

Person-to-person transmission is extremely rare. Although infrequent, sporadic human Q fever cases have occurred following contact with an infected parturient woman (in an obstetrician who performed an abortion on the pregnant woman) [42]. The infection can also be spread by the wind [43]. Thus, Q fever may occur in patients without any evident contact with animals.

**Q Fever in Animals**

*Coxiella burnetii* can infect a large number of animal species including livestock [33]. Infections in animals are usually asymptomatic and are not considered a veterinary problem. When clinical disease occurs, reproductive failure is usually the only symptom presented. Reproductive failure can be manifested as abortions, stillbirths, retained placenta, infertility, weak newborns and mastitis in dairy cattle. Anorexia and abortions have been reported more frequently in sheep and goats, while infertility, sporadic abortion and low birth weights are seen in cattle [44]. *C. burnetii* localises in the uterus and mammary glands of infected animals [33,45]. Epidemiological data indicate that dairy cows are more frequently chronically infected than sheep and thus may represent the most important source of human infection.

**Q Fever in Human**

Humans are the only species to develop symptomatic disease. The spectrum of illness in man is wide and consists of acute and chronic forms. The infectious dose is estimated to be 10 microorganisms or fewer [46]. The infections are primarily found in persons occupationally exposed, such as ranchers, veterinarians, and workers in meatpacking plants. Domestic ungulates, such as cattle, sheep, and goats, usually acquire and transmit *C. burnetii*; domestic pets (primarily cats) can be a primary source of human infection in urban environments [47,48]. The classic presentation is a flulike illness manifested by fevers, sweating, cough (productive at times), myalgias, and arthralgias. A high percentage of patients also have pneumonia and hepatitis. Pneumonia is typically mild, but progression to acute respiratory distress syndrome can occur [49]. Acute Q fever is found primarily as a granulomatous hepatitis. However, in patients infected by the aerosol route, Q fever pneumonia is more common. Life-threatening complications may
Diagnosis

The isolation of the pathogen is the gold standard but it remains time consuming and hazardous and therefore restricted to specialized laboratories [51]. Conventional diagnosis of Q fever is mainly based on serological tests such as immunofluorescence, enzyme linked immunosorbent assay and complement fixation test. For this reason, the enzyme-linked immunosorbent assay (ELISA) has been reported to be sensitive, easy to perform, with a potential for adoptability for automation, and can be applied in epidemiological surveys. It has been shown to be of value for the diagnosis of acute and chronic Q fever [53]. Currently, the polymerase chain reaction (PCR) is one of the most analytically sensitive and rapid means for both the direct detection of C. burnetii and the identification of shedders. PCR can be used on a wide range of samples (vaginal discharge, abortion material, faeces and milk (bulk or individual)). It has become increasingly common in diagnostic laboratories with PCR capability [54,55]. The level of detection of conventional PCR is related to the sample under investigation (1–500 bacteria/ml of milk; 1 bacteria/mg of faeces). Several target genes have been used, such as the multicopy insertion sequence (IS1111) or single copy genes encoding various proteins (e.g. dismutase [sodB]; com1 encoding a 27 kDa outer membrane protein; heat shock proteins [htpA and htpB]; isocitrate dehydrogenase [icd]; macrophage infectivity potentiator protein [chnp]). Real-time PCR techniques have also been described [56,57]. For routine diagnostics, it is generally accepted that real-time PCR technology is preferable to conventional gel-based detection methods. It allows high sample throughput, has a reduced potential for carry-over contamination and is best suited for quantification of C. burnetii in biological samples. Several typing methods have been used for the characterization of C. burnetii strains, including restriction endonucleases of genomic DNA [58], PFGE (pulsed-field gel electrophoresis) [59,60], and sequence and/or PCR-RFLP (restriction fragment length polymorphism) analysis of icd, com1 and mucZ genes. More recently, two PCR-based typing methods have been described, MLVA (multi-locus variable number of tandem repeats analysis) [52,61] and multispacer sequence typing (MST) [62]. These methods may become very useful for epidemiological investigations.

Prevention and Control

In case of Q fever outbreak, sanitary and prophylactic measures should be applied at herd and human level, in order to limit disease transmission. Human-to-human transmission is extremely rare and Q fever is mainly an airborne disease, measures of prevention are aimed at avoiding the exposure of humans and particularly persons at risk, to animal and environmental contamination. To prevent and reduce the animal and environmental contamination, several actions can be proposed. C. burnetii can be reduced in the farm environment by regular cleaning and disinfection of animal facilities, with particular care of parturition areas, using 10% sodium hypochlorite. In the UK, Health Protection Agency guidelines suggest the use of 2% formaldehyde, 1% Lysol, 5% hydrogen peroxide, 70% ethanol, or 5% chloroform for decontamination of surfaces [63]. Pregnant animals must be kept in separate pens, placenta and aborted fetuses must be removed quickly and disposed under hygienic condition to avoid being ingested by dogs, cats or wildlife. Spreading manure from contaminated farms in suburban areas and gardens should be avoided. In order to acquire and maintain Coxiella-free livestock, introduction of animals, regrouping of flocks, contacts with wildlife and infestation by ticks should be minimized. These methods may be effective in controlling disease but exposed animals may remain infected. Although vaccines for animal Q fever have been developed, there are not commercially available in most countries [32,66]. At human level, prevention of exposure to animals or wearing gloves and masks during manipulation of animals or their litter is advised [67].

Since Q fever is enzootic among wild and domestic animals, controlling C. burnetii infection in susceptible animals is difficult. The only way to really prevent the disease in ruminants is to vaccinate uninfected flocks, with an efficient vaccine. Vaccines can prevent abortion in animals and it is evident that a phase I vaccine must be used to control the disease and to reduce environmental contamination and thus, the risk of transmission to humans. The widespread application of such vaccine in cattle in Slovakia in the 1970s and 1980s significantly reduced the occurrence of Q fever in that country [68].

Finally, it is important to remember that C. burnetii is extremely hazardous to humans, and laboratory infections are common. Because of its ability to cause incapacitating disease in large groups of people, its low infectious dose, resistance in the environment, and aerosol route of transmission, C. burnetii is considered a potential agent of bioterrorism and is classified by the CDC as a group B agent. Appropriate precautions must be taken with these risk group 3 agents. Live culture or contaminated material from infected animals must only be handled in facilities that meet the requirements for containment group 3 pathogens.

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References

1. Marmion BP, Storm PA, Ayres JG, Semendric L, Mathews L, et al. (2005) Long-term persistence of Coxiella burnetii after acute primary Q fever. QJM 98: 7-20.
2. Derrick EH (1983) "Q" fever, a new fever entity: clinical features, diagnosis and laboratory investigation. Rev Infect Dis 5: 790-800.
3. Berri M, Souriau A, Crosby M, Crochet D, Lecchopier P, et al (2001) Relationship between the shedding of Coxiella burnetii, clinical signs and serological responses of 34 sheep. Vet Rec 148: 502-505.
4. Maurin M, Raoult D (2002) Update on Q fever, including endocarditis. Curr Clin Top Infect Dis 22: 97-124.
5. Arricau-Bouvery N, Hauch Y, Bejaoui A, Frangoulidis D, Bodier CC, et al. (2006) Molecular characterization of Coxiella burnetii isolates by infrequent restriction site-PCR and MLVA typing. BMC Microbiol 6: 38.
6. Burnet FM, Freeman M (1983) Experimental studies on the virus of "Q" fever. Rev Infect Dis 5: 800-808.
7. Philip CB (1948) Comments on the name of the Q fever organism. Public Health Rep 63: 58-59.
8. Maurin M, Raoult D (1999) Q fever. Clin Microbiol Rev 12: 518-553.
9. Raoult D, Marrie T, Mege J (2005) Natural history and pathophysiology of Q fever. Lancet Infect Dis 5: 219-226.
10. McCaul TF, Williams JC (1981) Developmental cycle of Coxiella burnetii. Structure and morphogenesis of vegetative and sporogenic differentiations. J Bacteriol 147: 1063-1076.
11. Coleman SA, Fischer ER, Howe D, Mead DJ, Heinzen RA (2004) Temporal analysis of Coxiella burnetii morphological differentiation. J Bacteriol 186: 7344-7352.
12. Heinzen RA, Hackstadt T, Samuel JE (1999) Developmental biology of Coxiella burnetii. Trends Microbiol 7: 149-154.
13. Angelakis E, Raoult D (2010) Q fever. Vet Microbiol 140: 297-309.
14. CFSPH (2007) Centre for Food Security and Public Health, Iowa state university, college of veterinary medicine 1-6.
15. Christie AB (1980) Q fever. Infectious Diseases: Epidemiology and Clinical Practice. New York: Churchill Livingstone.
16. Kaplan MM, Bertagna P (1995) The geographical distribution of Q fever. Bull World Health Organ 73: 829-860.
17. Arricau-Bouvery N, Rodolakis A (2005) Is Q fever an emerging or re-emerging zoonosis? Vet Res 36: 327-349.
18. Tissot-Dupont H, Raoult D, Brouqui P, Janbon F, Peyramond D, et al. (1992) Epidemiologic features and clinical presentation of acute Q fever in hospitalized patients: 323 French cases. Am J Med 93: 427-434.
19. Thomas D, Salmon, D, Smith R, Caul E, Treweek L, Kench, S, Coleman T, Hellenbrand W, Breuer T, Petersen L (2001) Changing epidemiology of Q fever in the UK. in: Kazar J, Toman R (eds.), Rickettsiae and rickettsial diseases. Slovak Academy of Sciences. Bratislava, Slovakia.
20. Yarov A, Slater P, Costin C (1990) Q fever in Israel. Public Health Rev 18: 129-137.
21. Siegman-Igra Y, Kaufman O, Keysary A, Rzotkiewicz S,  Shalit I (1990) Q fever in Israel. Public Health Rev 18: 129-137.
22. Yarrow A, Slater P, Costin C (1990) Q fever in Israel. Public Health Rev 18: 129-137.
23. Nalivaiko P, Ziese T, Schwartlander B, Matzdorf P, Kuhnhen C, et al. (1998) An outbreak of sheep-associated Q fever in a rural community in Germany. Eur J Epidemiol 14: 193-199.
24. Hellenbrand W, Breuer T, Petersen L (2001) Changing epidemiology of Q fever in Germany, 1947-1999. Emerg Infect Dis 7: 769-786.
25. Porten K, Rissland J, Tigges A, Broll S, Hopp W, et al. (2006) A super-spreading event infects hundreds with Q fever at a farmers' market in Germany. BMC Infect Dis 6: 147.
26. Psaroulaki A, Hadjichristodoulou C, Loukaides F, Soteriades E, Konstantinidis A, et al. (2006) Epidemiological study of Q fever in humans, ruminant animals, and ticks in Cyprus using a geographical information system. Eur J Clin Microbiol Infect Dis 25: 576-586.
27. Khallil M, Salkhaee E (2009) An update on a serologic survey of Q fever in domestic animals in Iran. Am J Trop Med Hyg 80: 1031-1032.
28. Kelly P, Matthwean L, Mason P, Raoult D (1993) Q fever in Zimbabwe. A review of the disease and the results of a seraosurvey of humans, cattle, goats and dogs. S Afr Med J 83: 21-25.
29. McQuiston JH, Childs JE (2002) Q fever in humans and animals in the United States. Vector Borne Zoonotic Dis 2: 179-191.
30. Dijkstra F, van der Hoek W, Wijers N, Schimmer B, Rietveld A, et al. (2012) The 2007-2010 Q fever epidemic in the Netherlands: characteristics of notified acute Q fever patients and the association with dairy goat farming. FEMS Immunol Med Microbiol 64: 3-12.
31. European Centre for Disease Prevention and Control (ECDC) Annual epidemiological report 2011. Reporting on 2009 surveillance data and 2010 epidemic intelligence data. Stockholm: ECDC.
32. European Food Safety Authority (EFSA) (2010) Panel on Animal Health and Welfare (AHAW), scientific opinion on Q fever. EFSA Journal 8: 1595.
33. Babudieri B (1959) Q fever: A zoonosis. Adv Vet Sci 5: 82-182.
34. Marrie TJ (1990) Epidemiology of Q fever. In: Marrie TJ (ed) Q fever, vol I: The disease. Boca Raton, CRC Press.
35. Rodolakis A, Berri M, Héchard C, Caudron C, Souriau A, et al. (2007) Comparison of Coxiella burnetii shedding in milk of dairy bovine, caprine, and ovine. J Dairy Sci 90: 5352-5360.
36. Guaittol R, Beauvial F, Berri M, Rodolakis A, Joly A, et al. (2006) Shedding routes of Coxiella burnetii in dairy cows: implications for detection and control. Vet. Res. 37: 627-833.
37. Grist NR (1959) The persistence of Q fever infection in a dairy herd. Vet Rec 71: 839-841.
38. DeLay PD, Lennette EH, Deome KB (1950) Q fever in California; recovery of Coxiella burnetii from naturally infected air-borne dust. J Immunol 65: 211-220.
39. Fishbein DB, Raoult D (1992) A cluster of Coxiella burnetii infections associated with exposure to vaccinated goats and their unpasteurized dairy products. Am J Trop Med Hgy 47: 35-40.
40. AFSSA (2004) "Fievre Q: rapport sur l’évaluation des risques pour la sant’e publique et des outils de gestion des risques en éveleage de ruminants," 1-88.
41. Rousset E, Duquesne V, Russo P, Thi‘ery R (2007) "Fievre Q: problk’ematiqkes et risques sanitaires," Bulletin de l’Academie Veterinaire de France 160: 107–114.
42. Raoult D, Stein, A (1994) Q fever during pregnancy— a risk for women, fetuses, and obstetricians. N Engl J Med 330: 371.
43. Tissot-Dupont H, Torres S, Nezni M, Raoult D (1999) A hyperendemic focus of Q fever related to sheep and wind. Am J Epidemiol 150: 67-74.
44. Ho T, Hixe KK, Yamasaki N, Zhang GQ, Ogawa M, et al. (1995) Isolation of Coxiella burnetii from dairy cattle and ticks, and some characteristics of the isolates in Japan. Microbiol Immunol 39: 663-671.
45. Martinov S (2007) Studies on mastites in sheep, caused by Coxiella burnetii. Biotechnology & Biotechnological Equipment 21: 484-490.
46. Tigert WD, Benenson AS, Gochenour WJS (1961) Airborne Q fever. Bacteriol Rev 25: 285-293.
47. Langley JM, Marrie TJ, Covert A, Waag DM, Williams JC (1958) Poker players’ pneumonia: an urban outbreak of Q fever following exposure to a parturient cat. N Engl J Med 319: 354-356.
48. Baca OG, Paretsky D (1983) Q fever and Coxiella burnetii: a model for host-parasite interactions. Microb Rev 47: 127-149.
49. Hartzell JD, Peng SW, Wood-Morris RN, Sarmiento DM, Colleen JF, et al. (2007) Atypical Q fever in US soldiers. Emerg Infect Dis 13: 1247-1249.
50. Milazzo A, Hall R, Storm PA, Harris RJ, Winslow W, et al. (2001) Sexually transmitted Q fever. Clin Infect Dis 33: 399-402.
51. Office International des Epizootics (OIE) Q fever. In: Manual of Diagnostic Tests and Vaccines for Terrestrial Animals 2004.
52. Slaba K, Skutlely R, Toman R (2005) Efficiency of various serological techniques for diagnosing Coxiella burnetii infection. Acta Virol 49: 123-127.
53. Embil J, Williams JC, Marrie TJ (1990) The immune response in a cat-related outbreak of Q fever as measured by the indirect immunofluorescent test and the enzyme-linked immunosorbent assay. Can J Microbiol 36: 229-296.
54. Berri M, Larauucu K, Rodolakis A (2000) The detection of Coxiella burnetii from ovine genital swabs, milk and fecal samples by the use of a single touchdown polymerase chain reaction. Vet Microbiol 72: 285-293.
55. Nicollet P, Valognes A (2007) Current review of Q fever diagnosis in animals. Bulletin De L Academie Veterinaire De France 160: 289-295.
56. Kim SG, Kim EH, Lafferty CJ Dubovi E (2005) Coxiella burnetii in Bulk Tank Milk Samples, United States. Emerg Infect Dis 11: 619-621.
57. Klee SR, Tyczka J, Ellerbrok H, Franz T, Linke S, et al. (2006) Highly sensitive real time PCR for specific detection and quantification of Coxiella burnetii. BMC Microbiol 6: 2.
58. Hendrix LR, Samuel JE, Malliav LP (1991) Differentiation of Coxiella burnetii isolates by analysis of restriction-endonuclease-digested DNA separated by SDS-PAGE. J Gen Microbiol 137: 269-276.
59. Heinzen R, Stiegler GL, Whiting LL, Schmitt SA, Malavia LP, et al. (1990) Use of pulse field gel electrophoresis to differentiate Coxiella burnetii strains. Ann NY Acad Sci 590: 504-513.

60. Jäger C, Willems H, Thiele D, Baijer G (1998) Molecular characterization of Coxiella burnetii isolates. Epidemiol Infect 120: 157-164.

61. Svraka S, Toman R, Skultety L, Slaba K, Homan WL (2006) Establishment of a genotyping scheme for Coxiella burnetii. FEMS Microbiol Lett 254: 268-274.

62. Glazunova O, Roux V, Freylikman O, Sekeyova Z, Fournous G, et al. (2005) Coxiella burnetii genotyping. Emerg Infect Dis 11: 1211-1217.

63. Chmielewski T, Sidi-Boumedine K, Duquesne V, Podsiajly E, Thiery R, et al. (2009) Molecular epidemiology of Q fever in Poland. Pol J Microbiol 58: 9-13.

64. Klaassen CH, Nabuurs-Franssen MH, Tilburg JJ, Hamans MA, Horrevorts AM (2009) Multigenotype Q fever outbreak, the Netherlands. Emerg Infect Dis 15: 613-614.

65. Health Protection Agency, 2010 at http://www.hpa.org.uk/deliberate accidental releases/biological.

66. Fournier P, Marrie TJ, Raoult D (1998) Diagnosis of Q Fever. J Clin Microbiol 36: 1823-1834.

67. Whitney EA, Massung RF, Candee AJ, Ailes EC, Myers LM, et al. (2009) Seroepidemiologic and occupational risk survey for Coxiella burnetii antibodies among US veterinarians. Clin Infect Dis 48: 550-557.

68. Kovacova E, Kazar J (2002) Q fever--still a query and underestimated infectious disease. Acta Virol 46: 193-210.