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## Review Article

# Q Fever in Domestic Small Ruminant

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### Abstract

Several bacterial pathogens cause abortion or fertility reduction in ruminant, some of which may also infect humans (zoonotic diseases). Query fever (Q fever) caused *C. burnetii*, which could be one of the causative agents and the main reservoir for the pathogen is domestic animals such as cattle, sheep and goats. This bacterium has a worldwide distribution and can infect a wide range of hosts, including domestic ruminants. The epidemiological data about geographic distribution of Q fever is limited. Moreover, the diagnosis of the *C. burnetii* is very difficult, because it need special stain in addition, it cannot be isolate on traditional media and isolate only on embryonated chicken eggs. The detection and diagnosis of coxiellosis in animal are necessary to reduce economic losses in animals and risk of transmission to human. Therefore, we reviewed the literatures on Q fever to highlight the epidemiology, diagnostic tests used in identifying *C. burnetii* and public health impact of Q fever as a basis for designing effective control strategies.

**Key words:** Q fever, *C. burnetii*, pathogenesis, diagnosis, complement fixation

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## INTRODUCTION

In 1935 in Queensland, Australia, an outbreak of a febrile illness of unknown origin (Query fever) was observed among abattoir workers and that is when Q fever was first acknowledged (Derrick, 1983). Q fever has been associated mostly with late abortion and reproductive disorders such as premature birth, dead or weak offspring endometritis and infertility in domestic ruminants (Maurin and Raoult, 1999; Kazar, 2005; Georgiev *et al.*, 2013). Infected animals usually shed the agent intermittently in milk, feces and urine with no outward signs of disease and should be regarded as possible sources of human infection (Guatteo *et al.*, 2011). Ticks may act as reservoirs of *C. burnetii* in nature, as they transmit the agent transstadially and transovarially to their progeny (Sprong *et al.*, 2012). *Coxiella burnetii* transmission by tick bite to animals has been proposed, but this is not the most important route of infection for livestock and it is still disputed in humans (Toledo *et al.*, 2009; Sprong *et al.*, 2012; Cong *et al.*, 2015).

The seroprevalence in ruminants was 17.4%, while displaying in different species as (32.7, 23.3 and 13%) for sheep, goats and cattle, respectively, whereas none of examining buffaloes was positive (Nahed and Khaled, 2012).

Q fever is typically an acute febrile illness with nonspecific clinical signs in humans, but hepatitis and atypical pneumonia are seen in severe cases and a small percentage of infected people will develop chronic infection with culture-negative valvular endocarditis (Kazar, 2005; Georgiev *et al.*, 2013). There are no specific clinical signs for the disease either in animal or in human, the laboratory diagnosis is the only accurate way to confirm the disease. The routine diagnosis of coxiellosis in aborted ruminants is to detect the pathogen using staining techniques, such as Stamp, Gimenez, Machiavello, followed by a serological analysis of at least ten sera samples by the Complement Fixation (CF) test, or better by ELISA (Kovacova *et al.*, 1998). However, staining techniques cannot be specific and they have reduced sensitivity, especially with vaginal swabs, milk and fecal sample (Berri *et al.*, 2000). Polymerase Chain Reaction is considered to be highly specific sensitive and rapid diagnostic tool for *C. burnetii*, compared to other laboratory techniques, since it can detect the smallest concentration of bacterial DNA in biological samples (Dehkordi, 2011).

The control of the disease has economic and health importance to reduce economic losses in animal and risk of transmission to human. It can be concluded that legislative

measures (e.g., culling of animals, banding movement and transport, mandatory vaccination) (Roest *et al.*, 2011) and improved biosecurity measures (e.g., avoiding contact between farm animals and visitors, quarantine of newly introduced animals and improved hygienic precautions of farm personnel) may also play roles in controlling *C. burnetii* infection (Paul *et al.*, 2012).

## ETIOLOGY

*Coxiella burnetii* is an intracellular, polymorphic bacillus (0.2-0.4 mm width, 0.4-1.0 mm length), which has a cell membrane, similar to Gram negative bacteria (Kovacova and Kazar, 2002). However, its stains poorly with pigmented Gram stain. Gimenez staining (Gimenez, 1964) is traditionally used to stain the pathogen from pathological materials and crops. *Coxiella burnetii* displays two antigenic phases, phase I and phase II, that are liable to the lipopolysaccharide (LPS) of the membrane. Phase I bacteria corresponds to the smooth phase (Smooth) of Gram negative bacteria and are more highly infectious and to phase II, to the granular phase (Rough) which has a lower virulence. Based on the Restriction Fragment Length Polymorphism (RFLP), strains of *C. burnetii* are grouped into six (I-VI) genomic groups (Hollenbeck *et al.*, 2015). The virulence and the pathogenicity of the *C. burnetii* are associated with genetic characteristics, plasmid groups and type of strains (Eldin *et al.*, 2014) and also with host factors such as pregnancy (Toman *et al.*, 2012).

## PATHOGENESIS

*Coxiella burnetii* has two morphologically distinct cell variants; an intracellular and metabolically active Large Cell Variant (LCV) and a spore-like Small Cell Variant (SCV) (McCaul and Williams, 1981). These two forms are morphologically and functionally distinct. The LCV is larger, elongated less electron-dense bacteria and metabolically active and replicating large bacteria (Bennett and Banazis, 2014). While, the SCV presents a compact rod-shaped with a very dense central region and it is considered the metabolically dormant and less replicating (Deretic, 2006). The SCVs are shed by infected animals. After infection the organism attaches to the cell membrane of phagocytic cells (Maurin and Raoult, 1999). After phagocytosis, the phagosome containing the SCV fuses with the lysosome (Williams and Thompson, 1991). The SCVs are metabolically activated in the acidic phagolysosome and can undergo vegetative growth to form LCVs (Maurin and Raoult, 1999; Roest, 2013). The LCVs and the activated SVCs

can both divide by binary fission (McCaul and Williams, 1981) and the LCV can also undergo sporogenic differentiation (Angelakis and Raoult, 2010). The spores that are produced can undergo further development to become metabolically inactive SCVs (Williams and Thompson, 1991; Van Schaik *et al.*, 2013) and both spores and SCVs can then be released from the infected host cell by either cell lysis or exocytosis (Maurin and Raoult, 1999). The entire development cycle of metabolically active *C. burnetii* takes place in acidic phagolysosomes; *C. burnetii* are resistant to microbicidal activities in the host macrophages (Mege *et al.*, 1997). The acidic environment also protects *C. burnetii* from the effects of antibiotics, as the efficacy of antibiotics is decreased in the acidic pH (Mege *et al.*, 1997). The SCV and spore forms are more difficult to denature than LCVs (Scott and Williams, 1990), possibly due to differences in cell wall composition and thickness as well as water content.

## EPIDEMIOLOGY

*Coxiella burnetii* infections in animals had gained very limited attention and it was considered to be an infection with very little impact on the health and production of domestic animals. Therefore, information on geographical distribution of animal coxiellosis was very limited. Epidemiological studies in animals suggested that *C. burnetii* infection is highly prevalent in tropical regions (Woldehiwet, 2004). The prevalence of *C. burnetii* infection in farm animals varies by host species and geographic area. Whereby, the prevalence estimates for cattle were up to 20.8% in Bulgaria, 15.0% in France, 19.3% in Germany, 21.0% in the Netherlands, for goats up to 40.0% in Bulgaria, 88.1% in France, 2.5% in Germany, 7.8% in the Netherlands and for sheep up to 56.9% in Bulgaria, 20.0% in France, 8.7% in Germany, 3.5% in the Netherlands, respectively (Georgiev *et al.*, 2013).

Surveillance of Q fever is mandatory in European Union countries during 2009, a total of 370 Q fever cases were reported in 24 EU countries, apart from the 2,317 cases from the 2009 outbreak in the Netherlands (Zarb *et al.*, 2012). The infection can occur in a wide range of vertebrates. The clinical forms of clinical infection mostly seen in humans. Whereas, the cattle, sheep and goats are the most source of human infection (De Bruin *et al.*, 2012). The infected animals can shed very high quantities of bacteria through amniotic fluid and foetal membranes. Milk is the most common shedding route for goats and cattle, whereas ewes shed bacteria most commonly in faeces and vaginal mucus (Rodolakis *et al.*, 2007).

The main route of transmission of the disease is inhalation of the bacteria from the infected environment and ingestion of contaminated food or water with discharge of infected animals (Roest, 2013). Also, animals, which live in or come in contact with contaminated premises or infected animals may acquire the infection (Bennett and Banazis, 2014).

Ticks may act as reservoirs of *C. burnetii* in nature, as they transmit the agent transstadially and transovarially to their progeny. *Coxiella burnetii* transmission by tick bite to animals has been proposed, but this is not the most important route of infection for livestock (Sprong *et al.*, 2012). Seasonality in the occurrence of *C. burnetii* infection was also reported in animals. In Japan, most of the Q fever cases in animals were reported in winter. On the other hand, in Germany most of the animal cases were reported in summer (Hellenbrand *et al.*, 2001) and in autumn in Cyprus (Cantas *et al.*, 2011).

The infection in most domestic animals remain unrecognized. In sheep, it causes usually abortion in last week of pregnancy, stillbirth or born weak live lambs. Abortion rate is usually low. The coxiellosis cause infertility in cattle but this outcome has not been reported in sheep (Roest, 2013; Bennett and Banazis, 2014).

## LABORATORY DIAGNOSIS

There are no specific clinical signs of *C. burnetii* infection in humans and animals. Therefore, laboratory diagnosis is the only way to confirm the disease. For laboratory diagnosis in the context of serial abortions and stillbirths, samples should be collected from aborted fetuses, placenta and vaginal discharges soon after abortion or parturition for detection and identification of *C. burnetii* in animals. If possible, vaginal swabs at the day of parturition (or taken less than 8 days after) should be collected in order to limit the number of false-negative PCR results. Milk from the tank, individual milk or colostrum, vaginal and faecal samples can be taken for investigating bacterial shedding (Sidi-Boumedine *et al.*, 2010).

**Isolation of the agent:** Due to the zoonotic nature of the agent, isolation of *C. burnetii* is not performed for routine diagnosis in veterinary medicine. The main reasons are the high level of expertise required, the time consumed and the requirement of BSL3 laboratories confinement (Berri *et al.*, 2000).

A simplified shell vial culture system traditionally used for virus isolation was proposed as an alternative technique

for the isolation of *C. burnetii* with increased sensitivity (Raoult *et al.*, 1990). Standard biological media are not suitable for the growth of *C. burnetii* (Kersh *et al.*, 2013).

Therefore, isolation of bacteria is 6-7 days old embryonated chicken eggs via the yolk sac. The inoculated eggs showing the death of embryos within 6-8 days post inoculation were harvested. The impression smears of infected yolk sac membranes harvested from chicken embryos were stained with Gimenez's stain for the microscopic demonstration of red inclusion bodies or elementary bodies of *C. burnetii*. The isolates were further confirmed by PCR (Vaidya *et al.*, 2008).

**Staining:** The routine diagnosis of coxiellosis in aborted ruminants is to detect the pathogen using staining techniques. Smears are usually stained by Stamp, Gimenez, Machiavello, or Giemsa stain (Gimenez, 1964; Angelakis and Raoult, 2010).

The presence of large masses of red-colored coccobacilli will indicate a strong presumptive diagnosis of *C. burnetii*. However, these diagnostic methods are poorly sensitive and not specific due to possible confusion with other pathogens such as *Brucella* spp., or *Chlamydia* spp. (Berri *et al.*, 2009). This followed by a serological analysis by the Complement Fixation (CF) test, or better by ELISA (Kovacova *et al.*, 1998). However, staining techniques cannot be specific and they have reduced sensitivity, especially with vaginal swabs, milk and a fecal sample (Berri *et al.*, 2000).

### Serological tests

**Enzyme-linked Immunosorbent Assay (ELISA):** The ELISA detects both phase I and phase II antibodies and provides a cumulative outcome of seropositive, suspect or seronegative status (Herremans *et al.*, 2013). The ELISA is preferred to IFA and CFT, particularly for veterinary diagnosis, because it is convenient for large-scale screening and as it is a reliable technique for demonstrating *C. burnetii* antibody in various animal species (Ezatkah *et al.*, 2015). Ready-to-use kits are commercially available and can detect anti-phase II antibodies or both anti-phase I and II antibodies. The IDEXX evaluated their ELISA test kit for *C. burnetii* uses small reference goat populations with known disease status as gold standard populations, although the method of disease status verification was not described. The IDEXX reported 100% sensitivity in their ELISA kit using 21 experimentally infected goats and 100% specificity using 44 goats from known negative herds. Even though, the ELISA test allows the testing

of a greater number of animals and flocks and despite the fact that it is a more sensitive test than the CF test and IFA (Berri *et al.*, 2002).

**Complement Fixation Test (CFT):** Although the CF test is prescribed by OIE as a diagnostic method for *C. burnetii*, its sensitivity is weak. Antibodies of *C. burnetii* in sheep and goats cannot be detected frequently by the antigen of the specific test (Horigan *et al.*, 2011). However, its use is now infrequent, as it has displayed a lower sensitivity than the ELISA (Herremans *et al.*, 2013). In ruminants, CFT can detect only IgG1 that fixes the complement. Moreover, IgG2, IgM and anticomplement substances potentially present in sera are capable of interfering with fixation of IgG1 to the complement lowering the titer of IgG1 detected by CFT (Rousset *et al.*, 2009).

Latent Class Analysis (LCA) has been used to estimate the sensitivity and specificity of the CFT (Hornstra *et al.*, 2011). The CFT had 56.4% sensitivity and 98.5% specificity for sheep and 20.6% and 97.3% for goats, respectively. Therefore, the sensitivity was poor compared to ELISAs which were tested using this same population (Natale *et al.*, 2012).

**Immunofluorescence Assay (IFA):** The species-specific indirect immunofluorescence assay (IFA) does not have the ability to screen in a large scale and it also cannot be automated and can be subjective. This is the reason why the diagnostic method IFA, which is considered as the gold standard in Q fever diagnosis in humans, is not preferred for a routine diagnosis of *C. burnetii* in animals. The IFA allows for the differentiation between a suspected acute or chronic clinical infection in humans, based on the ratio of phase I and phase II IgG antibodies (Wielders *et al.*, 2012). If the phase I titer is  $\geq$  phase II, the sample is indicative of a chronic exposure and if the phase II titer is  $>$  the phase I titer, the sample is indicative of an acute exposure. There is not yet any commercial kit using IFA for a veterinary investigation (Arricau-Bouvery and Rodolakis, 2005).

**Polymerase Chain Reaction (PCR):** The diagnosis of Coxiellosis in veterinary medicine was aided by the introduction of Polymerase Chain Reaction (PCR). Shedders could be identified whilst PCR kits are becoming available providing a specific, sensitive and rapid tool for the detection of *C. burnetii* in various clinical samples (Berri *et al.*, 2003).

Polymerase Chain Reaction is considered to be highly specific sensitive and rapid diagnostic tool for *C. burnetii*,

compared to other laboratory techniques, since it can detect the smallest concentration of bacterial DNA in biological samples (Willems *et al.*, 1994; Dehkordi, 2011). Insertion sequence IS1111 is one of the most commonly used primers in real time PCR for detection and quantification of bacterial DNA (Berri *et al.*, 2000; Angen *et al.*, 2011; Reisberg *et al.*, 2013).

Primers specific for the superoxide dismutase (*sodB*) gene; *com1* encoding a 27 kDa outer membrane protein; heat shock operon encoding two heat shock proteins (*htpA* and *htpB*); isocitrate dehydrogenase (*icd*); and macrophage infectivity potentiator protein (*cbmip*) are also used in PCR. A high degree of specificity has been shown by the primers specific to some plasmid mediated genes (*QpRs*, *QpH1*, *cbbE*) (Willems *et al.*, 1994), primers specific to the *htpAB*-associated repetitive element, superoxide dismutase gene (Stein and Raoult, 1992) and the 16s rRNA (Willems *et al.*, 1994).

**Molecular genotyping:** Molecular typing of pathogenic microorganisms is mainly used to study transmission routes and to assess sources of infection. Vaccination and the use of antibiotics may also interfere with the structure of bacterial populations and this can be evaluated by comparing molecular typing profiles of members of these populations. Genotypic characterization of *C. burnetii* is a prerequisite for surveillance purposes and for epidemiological investigation of Q fever outbreaks. The information is necessary to evaluate the epidemiological link between the source of the outbreak and human cases, with the final objective of establishing control measures in potential animal hosts involved in the life cycle (Astobiza *et al.*, 2012). The epidemiology of Q fever is complex due to the worldwide distribution, reservoir, vector diversity and lack of studies defining the dynamic interaction between these factors. Therefore, these tools are very useful for epidemiological investigation, particularly to clarify links regarding the source of infection, for better understanding the epidemiological emerging factors and to a lesser extent for evaluating control measures (Hornstra *et al.*, 2011). According to Astobiza *et al.* (2012), several techniques have been used to genotype and characterize and differentiate *C. burnetii* isolates based on the sequence analysis of certain genes such as *com1*, *icd* or *mucZ*. Pulsed field electrophoresis was able to classify *C. burnetii* isolates in different groups; DNA restriction fingerprints and separation by SDS-PAGE differentiated genomic groups.

More recently, two PCR-based typing methods have been described, multi-locus variable number of tandem repeats analysis (MLVA) (Arricau-Bouvery *et al.*, 2006; Svraka *et al.*, 2006) and Multispacer Sequence Typing (MST) (Glazunova *et al.*, 2005) that permit the typing of *C. burnetii*

without the need for isolation of the organism. Multispacer sequence typing is based on DNA sequence variations in 10 short intergenic regions and can be performed on isolated *C. burnetii* strains or directly on extracted DNA from clinical samples.

To date, MLVA and MST are considered to be the most discriminating methods for *C. burnetii*, allowing the identification of up to 36 distinct genotypes. The availability of such databases allows interlaboratory comparisons to be made easily and this will lead to a better understanding of the propagation of the *C. burnetii* isolates. Furthermore, their use in the characterization of field samples or isolates is increasing (Chmielewski *et al.*, 2009; Klaassen *et al.*, 2009).

## PREVENTION AND CONTROL

During outbreaks, some sanitary measures should be applied to reduce transmission of the disease within animals. changes in the farming practices including manure management such as covering and natural composting or ploughing of manure, treating manure with lime (or calcium cyanide (Roest *et al.*, 2011) and the removal of animal birth and abortion products (Georgiev *et al.*, 2013), disinfection of infected premises including paths and general environments of holding and the implementation of a farm animal breeding. However, the effectiveness of different control measures remains uncertain. It has been reported that the prevalence of *C. burnetii* in an infected herd usually declines over time, even without taking any control measures. This is probably due to the 'Natural' immunization of susceptible animals (Georgiev *et al.*, 2013).

Vaccinations have been shown to reduce abortion, shedding of *C. burnetii* and the occurrence of infection in animals. Outbreak vaccination, i.e., vaccinating herds that are already infected (Astobiza *et al.*, 2011) or otherwise under high infection pressure is less effective than regular vaccinations. Phase I vaccine is recommended for animals, as it is more protective than the phase II vaccine. The vaccination of animals was implemented during the outbreak in France during 2009 and in the Netherlands during 2007-2010 (De Bruin *et al.*, 2012).

## CONCLUSION

*Coxiella burnetii* is a widely distributed bacterium with zoonotic potentials. Since its first discovery in 1937, knowledge about this bacterium and the disease Q fever has increased quite a lot. However, there are still knowledge gaps which require further scientific studies. *Coxiella burnetii*

infection in domestic animals has been reported from almost all countries. Despite this, very little is known about the pathogenesis of *C. burnetii* infection in domestic animals.

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