Q fever: A Neglected Zoonotic Disease

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Abstract

Q fever has been identified as a global health concern and is reported by the OIE. *Coxiella burnetii* is the causative agent of the disease. Data on Q fever are available from many countries, and the disease is more common in regions with intensive livestock farming. Many domestic and wild animal species are susceptible to Q fever. Although there are no specific clinical findings in infected animals, it can cause issues such as abortion, infertility, and reduced yield, particularly in domesticated livestock. Infected animals can contaminate the environment and other healthy animals through animal products, aborted fetuses, and fetal fluids. Animals are widely recognized as the primary source of human infections. Human infection may occur in one of two ways: Inhaling contaminated air or consuming contaminated milk or dairy products. The risk is heightened when infected animals are shedding the bacteria, and direct contact with the animals may also lead to infection. Therefore, controlling the disease in animals should be a primary focus. A vaccine for Q fever is available, and the use of antibiotics in infected animals helps reduce *C. burnetii* shedding and the incidence of abortion. The disease is also treatable in humans, but early diagnosis is crucial.

Keywords: *C. burnetii*, Zoonotic disease, Epidemiology, Bacteriology, Diagnosis

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Introduction

History

The causative agent of the disease known as Q fever or coxiellosis is *Coxiella burnetii*. It was named "Q fever," with "Q" standing for "suspect" and "fever" for the characteristic fever (Derrick, 1937). In 1935, Edward Holbrook Derrick, director of the microbiology and pathology laboratory of the Queensland Health Organization, described a disease characterized by high fever and flu-like symptoms in slaughterhouse workers in Brisbane, Queensland, Australia (Derrick, 1937). This was the first time the disease had been documented in medical literature. Derrick sent infected guinea pig livers to Dr. Francis Macfarlane Burnet, a virologist, to establish infection in guinea pigs and mice. Dr. Burnet and Dr. Mavis Freeman succeeded in inducing febrile illness in experimental animals by injecting them with blood, urine, and infected guinea pig samples taken from Derrick's patients. An effective immune response was observed in the guinea pigs used as experimental animals. Dr. Burnet identified typical *Rickettsiae* in infected spleen preparations (Derrick, 1937). Researchers initially named the agent *Rickettsia burnetii* due to its intracellular localization and microscopic appearance (Burnet & Freeman, 1983).

In 1935, Gordon Davis and Dr. Herald Rea Cox established that *Dermacentor andersoni* ticks collected in the Nine-Mile region of Montana, USA, were carriers of pathogenic agents when administered to guinea pigs (Davis & Cox, 1938). The infected guinea pigs exhibited symptoms, including high fever, and an enlarged spleen. Cox designated this agent *Rickettsia diasporica* due to its resemblance to *Rickettsiae* and viruses. He cultivated the agent in embryonic chicken eggs (Davis & Cox, 1938). Meanwhile, during studies conducted at the Rocky Mountain Laboratory (RML), the blood of one of the laboratory workers who became ill was inoculated into guinea pigs, resulting in infection. The infectious agent was subsequently identified as pathogenic to humans. It was later demonstrated that *Rickettsia diaporica*, a bacterium isolated from ticks in the USA, was the same agent responsible for the disease described by Dyer as Q fever in humans in Australia. Around the same time, the name *Coxiella burnetii* suggested in honor of Cox and Burnet, who isolated the bacterium in the USA and Australia—was generally accepted (Dyer, 1938).

Etiology

Gram-negative, obligate intracellular, the standard measurements for *C. burnetii* typically range from 0.2 to 0.5µm in width and from 0.4 to 1.0µm in length (Qureshi et al., 2024). Classification of *C. burnetii* based on its 16S rRNA sequence places it within the phylum *Proteobacteria*, class *Gamma-Proteobacteria*, order *Legionellales*, and family *Coxiellaceae* within the order *Rickettsiales*. The total ratio of guanine and cytosine (G+C) is 42.2%, higher than that of other members of the order *Rickettsiales*. The genome size is approximately 2.0 to 2.2Mb (Maurin & Raoult, 1999; Drancourt & Raoult, 2005; Beare et al., 2009). *C. burnetii* has a biphasic developmental cycle that allows it to survive and maintain its infectiousness in the external environment while infecting susceptible hosts (McCaul and Williams, 1981). One of these developmental cycles is known as the large cell variant (LCV) and is the metabolically active form. Furthermore, LCV has a pleomorphic morphology is about 1 µm long and contains disorganized chromatin that can replicate inside the host cell. A small cell variant (SCV) that gives the agent spore-like

characteristics and arises as part of other developmental cycles. The SCV ranges from 0.2 to 0.5µm in length and its chromatin is denser (McCaul & Williams, 1981, Coleman et al., 2004; Kılıç & Çelebi, 2008; Sandoz et al., 2014). There is a lag phase approximately two days after infection, during which SCV differentiates into LCV. LCV then multiplies in a phase of exponentiation, which lasts about four days. The onset of the stationary phase signals the transition from LCV to SCV, with prolonged incubation (>14 days) resulting in vacuoles that harbor an almost homogeneous population of SCV (Sandoz et al., 2014). While their lipopolysaccharide (LPS) structure is mainly associated with SCV, it is also present in the LCV form. The antigenic variations depending on the LPS feature are called Phase I and II. The first phase, characterized by the presence of full-length LPS, is isolated from infected hosts, while the second phase contains a truncated or incomplete form of LPS lacking the 'O' antigen. Phase I is converted to Phase II by repeated serial passages (Kuley et al., 2015; Ullah et al., 2022).

Epidemiology

Q fever is a zoonosis. It is reported sporadically or in occasional outbreaks in many countries. The agent's spore-like form during its life cycle provides resistance to environmental conditions and imparts high virulence, enabling the disease to spread widely in nature. This characteristic enables the disease to affect a broad spectrum of animals, including domestic ruminants, as well as dogs, cats, birds, ticks, reptiles, and humans (Kılıç & Çelebi, 2008; Robi et al., 2023). Ticks play a role in transmitting the disease to susceptible hosts. It is widely acknowledged that ticks are the primary reservoir and vector of Q fever, and more than 40 tick species have been reported to be infected. *C. burnetii* was first reported in the USA in the tick species *Dermacentor andersoni*. The primary transmission routes in domestic animals are through the respiratory and digestive tracts. Vaginal secretions, feces, milk, and other animal waste from aborted animals or fetuses and fetal fluids contain high levels of the agent and play an important role in transmission. In addition, domestic animals are the main source of transmission of the disease to humans (Berri et al., 2002; Tagesu, 2019). Infected domestic ruminants have the potential to disseminate the pathogen to other susceptible hosts and the environment following abortion. It is therefore very important to determine the exact epidemiology of the disease in terms of protective control measures and diagnosis (Arricau Bouvery et al., 2003). The epidemiology of Q fever can be summarized in a transmission model. This is shown in Figure 1 (Roest et al., 2013).

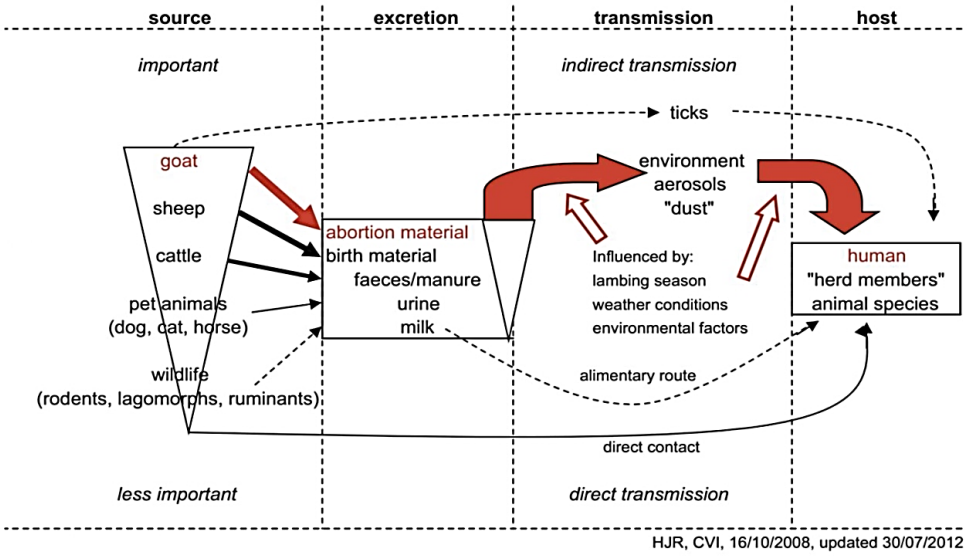

Fig. 1: Epidemiologic profile of *Coxiella burnetii*

When analyzing the incidence of Q fever in the world, the presence of infections has been reported in many countries. Notably, the spread of the disease worldwide varies according to geographical location (Arricau-Bouvery & Rodolakis, 2005). Considering that the disease is of animal origin, the potential of the disease is higher in regions where animal husbandry is intensive (Arricau-Bouvery & Rodolakis, 2005; Eldin et al., 2017). In addition to geographical location, the seasons have been found to impact the incidence of the disease. More cases of the disease have been reported in spring and summer when births occur. In settlements with dense animal populations, the rate of human infection is also higher in parallel. This is because domestic farm animals are the source of human infections. Animal owners, caretakers, wool processors, and people who produce and consume animal products, i.e. those in direct or indirect contact with animals and animal products are at risk of infection.
Similarly, laboratory personnel handling infected animal material, veterinarians, and veterinary technicians are also at significant risk (Kılıç & Çelebi, 2008).

Considering the cases occurring in urban centers, the spread of the infection is not limited to rural areas (Kılıç & Çelebi, 2008). It is thought that Q fever may be transmitted by cats and dogs in urban areas (McQuiston, et al., 2002; Ma et al., 2020).

Pathogenesis and Clinical Features of Q Fever

LPS in the Gram-negative cell wall structure of *C. burnetii* helps prevent the bacteria from being recognized by the immune system and maintains its pathogenic effects. LPS from *C. burnetii* exists in two phases. Phase I contains a complete LPS molecule that is virulent and can survive in monocytes and macrophages. Phase II is an avirulent form that arises after several generations of Phase I bacteria and has been shown to exhibit major chromosomal losses in the synthesis of the O-antigen sugars in the LPS structure (Hotta et al., 2002; Mertens & Samuel, 2007; Angelakis & Raoult, 2010).

Coxiella burnetii targets monocytes and macrophage cells (Angelakis & Raoult, 2010). After the agent enters the body, in its phase I form, it binds to phagocytic cells via the alphavbeta3 integrin, while in the Phase II form, binding is mediated by αvβ3 integrin and the complement receptor CR3. The fusion of the phagolysosome typically contains both phase variants of *C. burnetii*. However, Phase I forms can survive within phagocytic cells, whereas these cells destroy Phase II forms (Capo et al., 1999; Angelakis & Raoult, 2010). The acidic pH of the phagolysosome is highly favorable for the survival of pathogens. Crucially, the capacity of the organism to spread and replicate in the phagolysosome plays a key role in its ability to establish persistent infections. A metabolically active Phase I form completes its entire developmental cycle in this acidic vacuole (Roest, 2013; van Schaik et al., 2013; Ullah, 2022). This acidic pH provides the nutrients necessary for *C. burnetii* to grow and limits the effect of antimicrobials (Angelakis & Raoult, 2010).

In Animals

The disease caused by *Coxiella burnetii* in animals is called coxiellosis. This disease can affect many domestic and wild animal species, particularly ruminants such as cattle, sheep, and goats. However, most infected animals do not exhibit any specific clinical findings. The clinical findings that do occur in infected animals are as follows: *C. burnetii* colonizes the reproductive organs and mammary tissue of susceptible animals, progressing as a latent infection. If the animal becomes pregnant, the reactivated agent multiplies in the placenta and causes abortion in the final months of pregnancy (Woldehiwet, 2004). As with other bacterial diseases, infection is not apparent until an abortion occurs. Animals recover quickly after abortion and typically do not experience abortion in subsequent pregnancies (Berri et al., 2002; Arricau-Bouvery & Rodolakis, 2005; Kılıç & Çelebi, 2008). Abortion is a more prevalent occurrence in the ovine and caprine species than in bovine species. Abortions, particularly in small ruminants, manifest in the latter stages of pregnancy (Van den Brom et al., 2015). During pregnancy, the fetus and fetal fluids contain high levels of microorganism. The rate of postnatal spread of the agent to the environment is higher in ruminants like sheep and goats than in other animals (Shapiro et al., 2015; Freick et al., 2017; Ullah et al., 2022). Carnivores can become infected by consuming food contaminated with infected fetuses and fetal fluids or through inhalation (Agerholm, 2013). Some animals may experience postpartum problems or reduced milk production. In some cases, animals may display general symptoms of infection, such as fever, conjunctivitis, arthritis, and mastitis (Berri et al., 2002). A review of worldwide studies on the prevalence of Q fever in farm animals revealed that the seroprevalence of coxiellosis ranged from 15 to 27% in many countries, regardless of species. In their systematic review of 27 studies, Nokhodian et al. found a cumulative seroprevalence of 27% in animals.

In Humans

With a wide range of hosts, *C. burnetii* can survive in the environment for long periods. The disease can be caused by one or more of the highly infectious *C. burnetti*. *C. burnetii* is shed in feces, milk, and birth fluids of various infected animal species. It is the source of human infections. Infected animals shed large numbers of bacteria into the environment and the dried and aerosolized agent forms the basis of aerosol transmission (Robi et al., 2023). Acute and chronic forms of infection occur in humans (Sawyer et al., 1987). Host factors, such as age, immune status, and gender, are thought to influence the severity of the clinical form of the disease. For example, reported cases of disease in humans were analyzed. It was found that the disease is more common among adults than in children. Another example is that immunocompromised hosts are at greater risk of developing serious illness or chronic infection. Many human infections are asymptomatic. The clinical manifestations of the disease are non-specific and vary from one disease to another. The most common symptoms of the acute form include high fever, headache, muscle aches, chills, sweating, dry cough, nausea, vomiting, diarrhea, abdominal pain, and chest pain. Most people with an acute Q fever infection recover, but a few percent may develop serious complications involving the lungs, liver, heart and nervous system. Pregnant women who are infected may be at risk of premature birth or miscarriage. Very few human infections develop into chronic forms. The chronic form develops as a result of the progression of acute Q fever and may occur years later. The main clinical finding in the chronic form is endocarditis (Sawyer et al., 1987; Parker et al., 2006; Hartzell et al., 2008; Robi et al., 2023). Chronic Q fever is a serious illness and can be fatal if not treated correctly. Women infected during pregnancy may also be at risk of developing chronic Q fever. Minor valve abnormalities, such as bicuspid aortic valves, mitral valve prolapse, and mild valve regurgitation, have been linked to an increased risk of developing endocarditis (Parker et al., 2006; Song, 2015; Pratschke et al., 2016).

Diagnosis

It is extremely difficult to diagnose clinically because the symptoms are non-specific. (Niemczuk et al., 2014). *Coxiella burnetii*, an obligate intracellular agent, cannot grow on standard media. The isolation of the causative agent is prolonged, difficult, and dangerous. *C. burnetii* is characterized by its high degree of contagiousness, necessitating the implementation of Biosafety Level 3 (BSL3) containment protocols for its isolation (OIE, 2015). The isolation of the causative agent is regarded as the gold standard for diagnosing the disease. *C. burnetii* can be diagnosed from several biological samples, including placenta, vaginal mucus, milk, colostrum, feces, and various tissues and organs from aborted fetuses. Various methodologies have been developed for the identification of agents, including staining methods such as Stamp and Gimenez (Angesom et al., 2016). The diagnosis of Q fever is primarily based on several serologic tests. The immunofluorescent antibody testing (IFA) method is currently the reference standard for Q fever. It is capable of distinguishing antibodies against Phase variants. Another test, enzyme-linked immunosorbent assay (ELISA), has been documented as a highly sensitive and simple diagnostic method, adaptable to automation, and applicable in epidemiological surveys. With the increasing use of molecular techniques in diagnostics, disease agents can now be identified with high specificity and sensitivity in both clinical and environmental samples. Presently, the Polymerase Chain Reaction (PCR) is regarded as the most appropriate technique for the detection of *C. burnetii* in a variety of clinical samples (Berri et al., 2000; Gülmez Sağlam & Şahin, 2016).

Treatment

In Animals

The diagnosis of coxiellosis in animals is difficult due to the absence of characteristic clinical manifestations, which has resulted in a lack

of comprehensive therapeutic approaches to the disease. However, the disease can be managed through protective and control measures. Antibiotic treatment is recommended to reduce the number of abortions in infected animals and minimize the spread of *C. burnetii* during parturition. Prophylactic antibiotic treatment has the advantage of reducing the risk of abortion but is not decisive in eradicating the disease. Even if animals show clinical improvement after antibiotic treatment, they may continue to spread the causative agent (Kılıç & Çelebi, 2008). During coxiellosis-related abortions, parenteral administration of oxytetracycline has been shown to play a crucial role in preventing reproductive losses in animals. In ruminants, tetracycline treatments at 2-3 weeks intervals starting at 95 days of gestation can also help prevent yield losses due to other bacterial agents (Anderson, 2013; Ullah, 2022).

In Humans

The disease has two major clinical forms in humans: acute and chronic. *C. burnetii* is sensitive to antibiotics in the acute form, but in the chronic form, recovery is prolonged, and there is a risk of relapsing (Godinho et al., 2015; Pan et al., 2015). Acute Q fever may resolve spontaneously, but treatment is necessary to prevent complications and reduce the risk of progression to chronic infection. The initial three-day period following the onset of the disease is crucial, as prompt administration of treatment has been shown to reduce both the duration and severity of the disease. It is recommended that antibiotic treatment be initiated without awaiting serological diagnosis, as early intervention facilitates the expeditious resolution of the infection. The most effective antibiotics for treating acute Q fever include doxycycline, hydroxychloroquine, quinolones, chloramphenicol, rifampin, and macrolides. Doxycycline and hydroxychloroquine are typically used in combination, and the recommended duration of treatment is 2-3 weeks. Cotrimoxazole is regarded as a safe alternative for use during pregnancy and in pediatric cases (Maurin & Raoult, 1999; Kovacova & Kazar, 2002; Kılıç & Çelebi 2008; Schoffelen et al., 2015; Shah et al., 2015).

Tetracyclines can be used in the treatment of chronic form in humans. It is a standard treatment protocol that doxycycline and hydroxychloroquine are the preferred antibiotics for the treatment of endocarditis. Vascular infections are similarly treated with the same antibiotic, but such infections are typically treated for at least two years. The interruption of treatment has been demonstrated to result in the reappearance of clinical signs and disease. For chronic form in pregnant women, the treatment of choice is co-trimoxazole, while hydroxychloroquine and doxycycline are initiated postpartum. For children with endocarditis, surgical intervention is recommended in addition to antibiotic treatment (Anderson et al., 2013; Cross et al., 2016; Eldin et al., 2017; Miller et al., 2021).

Control

To implement effective protection and control measures, accurate epidemiological data are essential. The protective and control measures based on this data are crucial for preventing yield losses in animal husbandry and reducing the risk of human infections (Ullah, 2022). Given the low frequency of human-to-human transmission, the focus should be primarily on measures related to animals, which will play a key role in the success of an effective control program. Q fever is known to decline over time due to its self-limiting nature and the immunity developed against the causative agent. As animals are the primary reservoir of the disease, several measures can be implemented to prevent further spread. First, to protect herd health, new animals should be screened and confirmed to be healthy (Arricau-Bouvery & Rodolakis, 2005).

Controlling diseases in infected herds is crucial to protecting the environment, as well as animal and human health. To prevent the spread of infections within the herd, birthing compartments must be kept separate, postpartum disinfection procedures must be followed, and birthing equipment must be sterile. Anyone who has direct contact with animals giving birth should take necessary precautions, including wearing gloves, masks, and protective clothing. Aborted fetuses and birthing materials should be disposed of immediately. Additionally, waste should be kept from being eaten by wild or domestic carnivores. To prevent the disease from spreading to wider areas, the movement of infected herds should be restricted and maintained in an isolated environment. Fertilizer should be covered and treated with lime or 0.4% calcium cyanamide before application, and it should not be spread during windy weather (Arricau-Bouvery & Rodolakis, 2005; Shapiro et al., 2015; Van den Brom et al., 2015; Meadows et al., 2016).

Vaccination is one of the most important measures to prevent diseases. The OIE recommends the use of an inactivated Phase I vaccine, derived from the Nine Mile RSA 493 strain of *C. burnetii* isolated from ticks, in endemic regions. All inactivated phase I bacterial vaccines used for this purpose strongly reduce bacterial shedding in placentas and milk in experimental or natural Q fever infections in animals. However, it is suggested that vaccine efficacy is reduced in infected animals (Marmion et al., 1990; Arricau-Bouvery & Rodolakis, 2005; Schoffelen et al., 2013., OIE, 2015; Selim & Elhaig, 2016).

Conclusion

Q fever is a worldwide disease with significant health and socio-economic impacts due to its infections in both humans and many animal species. Considering the epidemiology of the disease, it becomes clear that especially domestic farm animals should be controlled. Because infected domestic animals are the main source of animal and human infections. Clinical signs of disease in humans and animals are insufficient to identify the disease. Therefore, the clinical findings may be confused with many other infections. As a result, the presence of Q fever can often be overlooked. In the diagnosis of obligate intracellular agents such as Q fever, it is possible to obtain real data on the disease, especially with the availability of recently developed serological and molecular methods. Q fever should be considered when assessing cases of the disease, and laboratory investigations should be carried out. The importance of controlling Q fever, one of the most important zoonotic infections, has been internationally recognized and emphasized by the World Health Organization (WHO) through the One Health approach. Interdisciplinary cooperation in the fight against Q fever is very important for a full understanding of the epidemiology of Q fever. Therefore, One Health-focused research and awareness raising is recommended, especially in areas with large numbers of animals and humans at risk.

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