

















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Navigating Q fever: Current perspectives and challenges in outbreak preparedness

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Abstract

Q fever, also known as query fever, is a zoonotic illness brought on by the *Coxiella burnetii* bacteria. This disease was first discovered in 1935 in Queensland, Australia. Worldwide, Q fever is a disease that requires notification, and certain nations classify it as a national health concern. A feature of *C. burnetii* is known as cell wall phase fluctuation. Serological testing is the main method used to diagnose Q fever illnesses. Inhalation is the primary method of *C. burnetii* transmission in both people and animals, with smaller amounts occurring through milk and milk product ingestion. The bacterial strain that is causing the infection determines how severe it is. Q fever is a significant zoonosis that can be dangerous for personnel working in veterinary laboratories, livestock breeding operations, and slaughterhouses due to its high human contagiousness. *Coxiella burnetii* is a biological weapon that can be sprayed on food, water, or even mail. It can also be employed as an aerosol. Antibiotics work well against this disease's acute form, but as the infection develops into a chronic form, treatment becomes more difficult and the illness frequently returns, which can result in a high death rate. Vaccination has been demonstrated to lower the incidence of animal infections, *C. burnetii* shedding, and abortion. Several hygienic precautions should be put in place during an outbreak to lessen the spread of disease to animals.

Keywords: Aerosol, *C. burnetii*, Public health, Q fever, Zoonosis.

Introduction

Q fever, also known as query fever, is a zoonotic illness caused by the *Coxiella burnetii* bacteria (Ullah *et al.*, 2022). *Coxiella burnetii* is a Gram-negative γ -proteobacterium that is a member of the

Coxiellaceae family and the Legionellales order of bacteria (Ohlopkova *et al.*, 2023). The Q fever disease can infect dogs, cats, birds, fish, reptiles, arthropods, people, ruminants, and rodents (Porter *et al.*, 2011). Domestic ruminants, such as cattle, sheep, and goats, are

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commonly thought to be the primary reservoir of these infections (Robi *et al.*, 2023). During intraperitoneal infection tests, this disease was found to be extremely infectious in experimental rabbits (Eldin *et al.*, 2017). Q fever was first reported in Australia in 1935 and then spread throughout the world until now (Celina and Cerný, 2022). The understanding of this illness and *C. burnetii*, the causal culprit, has advanced dramatically in recent years. In most nations where systematic serology is conducted, *C. burnetii* is acknowledged as a global cause of endocarditis (Bozza *et al.*, 2023). Q fever may be a widespread cause of fever in intertropical zones, according to research conducted in tropical regions and recent wars in the Middle East (Ahmadinezhad *et al.*, 2022). Since the 2007 outbreak in the Netherlands, where the disease sickened over 4,000 people, Q fever has become more relevant to public health in the past 10 years (Bronner *et al.*, 2020).

Aerosols tainted with bacteria are the most frequent means of Q fever transmission (Miller *et al.*, 2021). The pathogenic bacterium that causes this disease, *C. burnetii*, is highly contagious and spreads through aerosol, making it potentially employed as a biological weapon (Dragan and Voth, 2020). For this reason, prompt and appropriate treatment is required in the event of an outbreak. Wind can help the bacteria travel away from the main site of infection, putting people who live close to rural regions or have direct contact with domestic ruminants at greater risk of getting this bacterial infection (Clark and Magalhães, 2018). Though it is uncommon, human transmission of *C. burnetii* infection can occur through ticks' bites and the consumption of unpasteurized milk or cheese (Abdali *et al.*, 2018).

Human Q fever manifests as an acute fever with symptoms resembling those of influenza, frequently accompanied by lung inflammation or pneumonia (Miller *et al.*, 2021). In contrast, Q fever is frequently subclinical in animals (Ullah *et al.*, 2022). Severe Q fever can cause fatal conditions such as liver failure, brain inflammation, blood vessel abnormalities, inflammation of the bones, and endocarditis, an infection of the heart that frequently results in death. Additionally, severe Q fever is a common cause of abortion and infertility in ruminant animals (Miller *et al.*, 2021). According to recent studies, pulmonary lesions can result from the aerosol transmission of Q fever (Gregory *et al.*, 2019). The development of quick and precise Q fever diagnosis is still ongoing in wealthy nations.

Due to its effects on human health, cattle's responsiveness to interventions, clinical severity, and emergencies, Q fever has become a serious worry as it has spread around the world, especially in developing countries (Toledo-Perona *et al.*, 2024). Despite being a worldwide health concern, Q fever is underreported, and disease surveillance is frequently disregarded. So the aim of this review article is to explain the

etiology, history, epidemiology, pathogenesis, clinical symptoms, diagnosis, transmission, risk factors, public health importance, potential as bioterrorism, treatment, vaccination, and control of Q fever.

Etiology

Coxiella burnetii is a Gram-negative γ -proteobacterium that reproduces only inside cells (Sireci *et al.*, 2021). Prior names for *C. burnetii* were *Rickettsia diaporica* and *Rickettsia burnetii* (Gürtler *et al.*, 2014). The organism's present name commemorates its discoverer and indicates its minuscule size. Despite having historically been related to *Rickettsia*, *C. burnetii* is currently classified by gene sequence analysis in the family Coxiellaceae, order Legionella (Ohlopkova *et al.*, 2023). As a result, *Coxiella* is distinct from ordinary *Rickettsia* in a few aspects.

Coxiella burnetii is a $0.3 \times 1.0 \mu\text{m}$ coccobacillus that exhibits significant pleomorphism (Shaw and Voth, 2019). The outer and inner membranes of this organism's envelope are each 6.5 nm thick. There is a layer of peptidoglycan between the two membranes (Shepherd *et al.*, 2023). Although *Coxiella* is categorized as Gram-negative, staining might be a Gram variable based on the mutation (Eldin *et al.*, 2017). The fact that this bacteria can cause illness makes it one of the most contagious organisms. These bacteria can also persist in the environment for long periods of time due to their great stability (Anastácio *et al.*, 2022). *Coxiella* is an intracellular pathogen that survives in phagolysosomes with a pH of 4.8. In these environments, it can survive in infected cells without endangering their viability (Samanta *et al.*, 2019).

The developmental cycle of *C. burnetii* consists of two stages: transverse binary fission and sporulation (Tagesu, 2019). Because of its spore-like shape, it is resistant to heat and disinfectants and has a very extended environmental life span (Pexara *et al.*, 2018). This spore-like appearance differs from the typical spores found in Gram-positive species. The DNA is filled with a protein that resembles histone Hc1 in the ground body of *Chlamydia trachomatis* but lacks the cysteine-rich spore coat and dipicolinic acid present in spores of Gram-positive bacteria (He *et al.*, 2024).

The two morphological forms of *Coxiella*, giant and small, are shown by electron microscopy (Sitdikov *et al.*, 2020). This phenomenon differs from the phenomena of phase variation and an organism's developmental phases. Host cells consume *Coxiella* in its tiny variant form. Phagosomes that contain the organism fuse with the main lysosomes (Wallqvist *et al.*, 2017). Because phagolysosomes have an acidic pH, *C. burnetii* enzymes are activated and big-cell variants are developed. These variants can then form spores that are extremely resistant. There have been descriptions of six different strain types: Dod, Biothere, Hamilton, Bacca, Rasche, and Corazon (Long *et al.*, 2019).

History

In August 1935, the Queensland Department of Health in Brisbane, Australia, ordered Dr. E. H. Derrick, the Director of the Microbiology and Pathology Laboratory, to look into a “fever-like” disease outbreak among its abattoir workers that went untreated (Ullah et al., 2022). The illness he called “Q” for “Query fever”; “Q” for “Queensland”. Derrick injects blood or urine from “Q” fever sufferers into guinea pigs. The guinea pig then developed a fever (Sam et al., 2023). Derrick sent a salt emulsion of diseased guinea pig livers to Macfarlane Burnet in Melbourne after failing to identify the agent causing the sickness. It was possible for Burnet to separate organisms that “seemed to be rickettsial” (Gürtler et al., 2014). Nearly simultaneously, researchers at Rocky Mountain Laboratory in Montana, Drs. Herald Rea Cox and Gordon Davis, are investigating potential hay fever and tularemia vectors found in the Rocky Mountains. Davis fed guinea pigs fleas, which are thought to be the vector, causing the guinea pigs to become ill (Christodoulou et al., 2023).

Dr. Rolla Dyer, the director of the National Institutes of Health, went to see Cox in Montana in May 1938 in order to refute Cox’s claim that he had grown a significant amount of rickettsiae in embryonated eggs. He became unwell 10 days later, experiencing fever, chills, sweats, and retro-orbital pain. Guinea pigs given 5 ml of blood on the sixth day of sickness developed a fever after the injection (Dzul-Rosado et al., 2013). Studies conducted later revealed that this agent was the same as the Nine Mile agent that was separated from ticks (Dragan and Voth, 2020). Burnet delivered Dyer mice’s spleens in April 1938, and Dyer demonstrated that the Q fever agent was the same as the Nine Mile agent (Eldin et al., 2017). To reflect the filterable qualities of the Nine Mile agent, Cox gave it the name *Rickettsia diaporica* (diaporica means having the property or ability to pass through) (Vellema et al., 2021). Meanwhile, Derrick proposes *R. burnetii* as the name of the Q fever agent in Australia (Gürtler et al., 2014). Since it seemed that *R. burnetii* was different from other rickettsiae in 1948, Cornelius B. Philip suggested that this organism be regarded as a solitary species within its own genus (Sam et al., 2023). He recommended *Coxiella* as a name. The Q fever agent is now known as *C. burnetii* (Ullah et al., 2022). In 1986, Cox and Burnet passed away.

Epidemiology

Infected ruminants are usually the main source of infection in most Q fever outbreaks, and the number of cases is directly connected to the local livestock population (Celina and Cerný, 2022). Pet animals, particularly dogs and cats that are kept in close proximity to their owners, are recognized to be significant reservoirs of *C. burnetii* during urban Q fever outbreaks, aside from livestock (Ma et al., 2020). It has been hypothesized that dogs and cats

may become infected through tick bites, eating raw meat, drinking milk from infected animals, breathing in aerosolized bacteria from the environment, or preying on contaminated animal species, even though the primary causes of infection in pets are still poorly understood (Cyr et al., 2021).

Although less common than in livestock, *C. burnetii* infections have been documented in other domestic mammals, such as horses, pigs, camels, rabbits, water buffalo, rats, and mice (Celina and Cerný, 2022). There have been numerous reports of serological evidence of *C. burnetii* infection in horses thus far (Akter et al., 2020; Khademi et al., 2020). Horses are reservoirs for *C. burnetii*, although their epidemiological significance has not been sufficiently investigated.

Numerous wild species, both captive and in the wild, are home to *C. burnetii*, which has been linked to the spread of Q fever. Starting with birds, infections with *C. burnetii* have been reported in both farm and pet birds (Ebani and Mancianti, 2022). These include barn common quail, swallows, Eclectus parrots, turkeys, pheasants, wood-pigeons, pigeons, Italian sparrows, rooks, Eurasian reed warblers, carrion crows, ravens, house sparrows, white wagtails, redstarts, western yellow wagtails, Japanese quail, black-headed gulls, common terns, hooded crows, common starlings, black kites, magpies, wild ducks, Eurasian griffon vultures, fieldfare, thrush nightingale, willow warblers, common blackbirds, turtle doves, great white pelicans, and wood sandpipers (Celina and Cerný, 2022).

Coxiella burnetii was discovered in several earlier studies on reptiles, where the bacterium was seropositive in snakes and tortoises (Sander et al., 2021; Mendoza-Roldan et al., 2023). Numerous mammal species have been shown to be infected with *C. burnetii*. Cervids, such as white-tailed deer, California mule deer, black-tailed deer, and Rocky Mountain mule deer in the United States, have been found to harbor *C. burnetii* (Kirchgeßner et al., 2013). Among the European cervids that have been documented to be affected include fallow, red, and roe deer (Ruiz-Fons et al., 2008). Additionally, reports of Sika deer displaying serological indications of infection have been made from Japan (Ejercito et al., 1993).

Moreover, hares, numerous rodent species, and wild boars have all been found to harbor *C. burnetii*. In the domestic cycle of *C. burnetii*, rodents are thought to be important reservoirs of infection. Several rodent species have been linked to coxiellosis in livestock (Mangombi-Pambou et al., 2023). Furthermore, *C. burnetii* has been linked to reproductive losses in exotic ungulates kept in captivity, such as sable antelopes, waterbucks, and numerous gazelles, including dama gazelle, Cuvier’s gazelle, and arbor gazelle (González-Barrio and Ruiz-Fons, 2019).

In addition to land mammals, marine animals such as sea otters, northern fur seals, steller sea lions, and harbor seals have been shown to contain *C. burnetii*

(Minor *et al.*, 2013). Coyotes, wild cats, jaguars, red foxes, western grey kangaroos, common genet, North African hedgehogs, and Amur hedgehogs are among the other mammals that have been found to carry *C. burnetii* (Celina and Cerný, 2022).

Q fever is a disease that requires worldwide notification (except from New Zealand), and certain nations classify it as a national health concern (Salifu *et al.*, 2019). The prevalence varies significantly across nations as a result of potential subnotification and epidemiological gaps. Q fever occasionally breaks out in endemic areas, usually following the completion of dangerous tasks like employment in slaughterhouses or agriculture (Epelboin *et al.*, 2021). It is believed that ticks or other arthropods carry the disease, with domestic animals serving as a secondary reservoir despite wild animals being the primary reservoir (Eldin *et al.*, 2017). From 2003 to 2017, there were 400–600 cases reported annually in Australia (Miller *et al.*, 2021).

In 1940, 15 people were infected in the United States after the start of the Q fever study at the National Institutes of Health. Then, in 1946, the illness struck 47 individuals in the same area (Dragan and Voth, 2020). Since not all affected individuals work directly with the disease, it is thought that improper handling of the bacteria is what caused the agent to be released into the facility's air in these cases. Cases in the nation were first reported to the Centers for Disease Control and Prevention in 1999; between 2016 and 2018, there were between 164 and 215 cases reported (Cho *et al.*, 2023).

In 1955, nine nations in Africa reported differing numbers of cases of Q fever, making it the third continent to be documented with the illness (Sadiki *et al.*, 2023). The disease arrived in South America that same year, with the first case being reported in a slaughterhouse in Cayenne, French Guiana (Thill *et al.*, 2022). South America has long experienced sporadic instances; in 2005, there were 150 cases per 100,000 people (Fernandes and de Lemos, 2023).

The Netherlands experienced the greatest Q fever outbreak in history between 2007 and 2010. There have been at least 4,000 acute cases and an estimated 40,000 total illnesses as a result of the seasonal outbreak (van der Hoek *et al.*, 2012). The sick individuals were not all directly involved with animals, but many were situated near dairy farms (Byeon *et al.*, 2022). When public health initiatives were ineffective, it was determined to methodically kill pregnant animals, which resulted in the slaughter of over 50,000 animals (Schneeberger *et al.*, 2014). Animal vaccinations are used to control this disease.

Pathogenesis

A feature of *C. burnetii* is known as cell wall phase fluctuation (Beare *et al.*, 2018). Phase I bacteria are extremely pathogenic and possess whole lipopolysaccharide (LPS) molecules (Williams-Macdonald *et al.*, 2023). It is possible to separate this

lethal strain of the bacteria from infected humans, animals, and fleas. However, Phase I bacteria can be serially passed in chicken embryonates or in cell culture to produce Phase II bacteria, which are avirulent (Sireci *et al.*, 2021). Stage II LPS is abrasive and jagged. The two antigenic variants of *C. burnetii* have different cell densities, surface charges, and surface protein configurations in addition to LPS (Howe *et al.*, 2010). There are two distinct morphological forms of *C. burnetii*: the small-cell variant (SCV) and the large-cell variant (LCV) (Sobotta *et al.*, 2017). LCV is larger and has fewer electron-rich centers than SCV, which is a less replicative and metabolically inactive form with a compact rod shape and a dense core region (Claudel *et al.*, 2020). Environmental pollution results from the discharge of this SCV by diseased animals (Gerba, 2015).

Inhalation is the primary method of *C. burnetii* transmission in both people and animals, with smaller amounts occurring through milk and milk product ingestion (Knobel *et al.*, 2013). Bacteria adhere to the cell membranes of phagocytes (monocytes/macrophages) once they have entered the body. While integrin $\alpha_v\beta_3$ and the complement receptor CR3 mediate the attachment of avirulent bacteria to phagocytic cells, integrin $\alpha_v\beta_3$ starts the attachment of virulent bacteria to these cells (Walbaum *et al.*, 2021). Phagocytic cells allow phase I bacteria to persist, whereas phase II bacteria are destroyed. Furthermore, host cells phagocytose many fewer Phase I bacteria than Phase II germs (Howe *et al.*, 2010).

Monocytes and macrophages phagocytose SCVs, which then enter the phagolysosome (Szulc-Dąbrowska *et al.*, 2020). Here, the SCV merges with the lysosomal contents, changes into a form that is metabolically active, grows vegetatively, and eventually becomes the LCV. Normally, this phagolysosomal niche contains both antigenic variants of *C. burnetii* (Sobotta *et al.*, 2016). Nevertheless, Phase II bacteria were promptly eradicated. *C. burnetii* grows particularly well in the acidic environment of phagolysosomes (Kodori *et al.*, 2023). The organism's propensity to acquire chronic infections and its capacity for reproduction in acidic phagolysosomes are particularly significant. This acidic niche is where metabolically active Phase I bacteria complete their whole developmental cycle (Shepherd *et al.*, 2023). Because of its acidic pH, *C. burnetii* can grow and thrive while being shielded from the harmful effects of many antimicrobials (Smith *et al.*, 2019).

The function of host cellular immunity in infected human patients is not well understood. Specific IgG and IgM Phase II antibodies can be detected in goats' blood 2 weeks after infection, and their titers can stay elevated for up to 13 weeks. This is indicative of the immunological response of goats to *C. burnetii* infection (Muleme *et al.*, 2017). After 4 weeks of Phase II antibodies, Phase I antibodies appear. The immunological response to *C. burnetii* can linger

anywhere from a few months to several years (Kersh *et al.*, 2013). The primary source of metabolically active LCV is placental trophoblasts (Gauster *et al.*, 2022). During an acute infection, the organism is found in the host's lungs, liver, spleen, and blood (Anastácio *et al.*, 2022). In non-pregnant animals, the condition is primarily asymptomatic; however, in pregnant animals, the most significant clinical signs are abortion, stillbirth, weak offspring birth, and premature birth (Plummer *et al.*, 2018). Q fever infection may be the cause of respiratory and intestinal issues in otherwise healthy youngsters living in high-risk locations (Ullah *et al.*, 2022). While Q fever rarely results in reproductive problems in domestic animals, it has been known to cause up to 90% more abortions in goats (Agerholm, 2013).

Human infections caused by *C. burnetii* can manifest as either acute or chronic. Chronic Q fever can be fatal in many cases when combined with chronic endocarditis, while acute infections usually go away on their own with mild flu-like symptoms (Das *et al.*, 2014). The fetus normally appears fresh and normal in abortions caused by *C. burnetii* infection; however, occasionally the fetus turns necrotic (Álvarez-Alonso *et al.*, 2018). There is macroscopic placental inflammation in the badly damaged intercotyledonous gaps, accompanied by a purulent brownish-yellow exudate (Zarza *et al.*, 2021). Under a microscope, the most impacted trophoblast cells are those found in the intercotyledonary region of the allanto-chorion and at the base of the villi (Roest *et al.*, 2012). This inflammation might present as chronic necrosis with pus-like discharge or as modest mononuclear infiltration. The basophilic intracytoplasmic granulations and foamy vacuolated cytoplasm are frequently observed in the epithelial cells located in the chorionic membrane at the base of the villi (Purnamiharja *et al.*, 2023). Several fetuses had liver inflammation and moderate granulations on the histopathological investigation. Yet, it was discovered that other organs appeared normal (Lee *et al.*, 2012).

Clinical symptoms

Clinical symptoms in humans: Humans infected with *C. burnetii* can exhibit both acute and persistent clinical symptoms. Nonetheless, some patients develop severe illness, and 60% of infections are asymptomatic (Ghaoui *et al.*, 2023). Depending on the mode of infection, Q fever takes 2 to 3 weeks to incubate (Knobel *et al.*, 2013). Acute Q fever symptoms are nonspecific and differ from patient to patient. The most common clinical presentation is a self-limiting febrile fever with accompanying severe headache, arthralgia, myalgia, and cough (Finn *et al.*, 2021).

A prolonged fever, which can reach 39°C–40°C, typically lasts for 2–4 days before progressively returning to normal over the following 5–14 days (Sam *et al.*, 2023). Atypical pneumonia is yet another typical sign of severe Q fever (Honarmand, 2012). The symptoms of mild pneumonia typically include

a dry cough, fever, and little respiratory discomfort (Kelm *et al.*, 2017). Additionally, patients may develop subclinical hepatitis, granulomatous hepatitis with persistent fever, and hepatitis with hepatomegaly but without jaundice (Lee *et al.*, 2012). Hepatitis typically develops in immunocompromised young children, but pneumonia typically affects older patients (Eldin *et al.*, 2017).

Pericarditis may coexist with myocarditis, which affects 2% of individuals with acute illness (Jacobson and Sutthiwan, 2019). Acute Q fever cases have also been linked to skin rashes and neurological conditions such as meningoencephalitis and encephalitis, lymphocytic meningitis, and peripheral neuropathy (Gu *et al.*, 2022). Pregnant-infected women may experience spontaneous abortion, intrauterine fetal death, early birth, or stunted fetal growth (Mbousou *et al.*, 2019). Women who are pregnant have the potential to become chronically infected and lose their babies in later pregnancies. In the acute stage of the illness, death is an uncommon result. However, myocarditis and acute respiratory distress can be fatal (Honarmand, 2012).

Chronic Q fever is characterized as an infection that lasts longer than 6 months after the sickness first appears (Buijs *et al.*, 2021). In less than 5% of cases, this happens. Endocarditis is the primary clinical manifestation of this type of illness (Bozza *et al.*, 2023). In 60%–70% of all chronic cases, this happens. Patients receiving antibiotic treatment have a death rate of less than 10% in cases of Q fever endocarditis (Kampschreur *et al.*, 2012). Usually, the mitral and aortic valves are impacted. Non-specific symptoms could include weakness, exhaustion, anorexia, heart failure, intermittent fever, or weight loss (Ramos *et al.*, 2023). Additional symptoms include clubbing, purpuric rash, hepatomegaly, splenomegaly, osteomyelitis, osteoarthritis, and arterial embolism (Monteiro *et al.*, 2021).

Clinical symptoms in animals: The majority of animal infections have no symptoms. During acute experimental infections, the organism is detected in the blood, lungs, liver, and spleen; however, chronically infected animals continuously excrete the germs on their faces and urine (Porter *et al.*, 2011). The majority of pet infections are still unclear. It is believed that Q fever contributes to pet reproductive issues and abortions (Eldin *et al.*, 2017). Scientific data backs up the theory that *C. burnetii* can spread epidemics of infertility in sheep and goats but not in cattle (García-Ispuerto *et al.*, 2014). Endometritis, metritis, stillbirth, low birth weight, and infertility are examples of reproductive problems in pets (Agerholm, 2013).

Coxiella burnetii antibody levels in bulk tank milk from Danish dairy cows were not linked to stillbirth or prenatal mortality rates in herds (Nielsen *et al.*, 2011). Sheep and goats have comparatively greater abortion rates than cattle (Cantas *et al.*, 2011). Both sheep and cows typically have abortions at the end of

their pregnancies. The aborted fetus seems normal in the majority of abortion instances. Infected placentas may exhibit fibrous thickening of the intracotyl and discolored exudates (Ullah *et al.*, 2022). In goats and cattle, the most commonly reported clinical symptoms are severe myometrial inflammation and metritis (Robi *et al.*, 2023).

Diagnosis

Serological testing is the main method used to diagnose Q fever illnesses. Although there are numerous laboratory studies available, the immunofluorescence test is the most widely used approach for antibody detection because of its high sensitivity and specificity (Gutiérrez-Bautista *et al.*, 2024). The use of polymerase chain reaction (PCR), a promising test that may even be able to identify *C. burnetii* in the early stages of the illness, is presently restricted to research and reference labs. The molecular detection of *C. burnetii* in blood and tissue samples using conventional PCR involves targeting and sequencing the transposase gene insertion element, IS1111, of *C. burnetii*. PCR and sequencing of the IS1111 gene help in achieving a short turn-around time for results, including high specificity (Bae *et al.*, 2019).

Regular Giemsa staining can be used to generate frozen tissue or smears that display *C. burnetii* (Honarmand, 2012). Though not unique to Q fever, the occurrence of donut granulomas, or fibrin rings, in histopathological specimens is traditionally linked to the illness (Carvalho *et al.*, 2021). There are a number of issues with culture or visualizing the organism, even when isolation of the organism yields a conclusive diagnosis. Since *C. burnetii* is highly contagious and might be used as a bioterrorism weapon, most clinical laboratories do not culture it due to its technical difficulty and requirement for level 3 biosafety procedures (Francis *et al.*, 2020). Consequently, it is not recommended to isolate the organism in settings without sufficient security.

Serological procedures are the preferred diagnostic procedure since they are safer and simpler than isolation attempts. ELISA methods, one of the serological procedures, are widely recognized and used in the diagnosis of acute and chronic *C. burnetii* infection (Gutiérrez-Bautista *et al.*, 2024). The ELISA technique has arrays of advantages, such as its ease of execution, objective interpretation, and potential for automation; thus, making it a suitable screening option, especially when analyzing a large number of samples and also for epidemiological studies. However, some inconsistent results have been reported while using different ELISA kits (Horigan *et al.*, 2011; Gutiérrez-Bautista *et al.*, 2024). One option is to use multiple kits to determine the status of a serum. Additionally, available serological methods do not have the capability to distinguish between infected and vaccinated ruminants (Gutiérrez-Bautista *et al.*, 2024). Phase I and II antibody detection are the most often utilized serological tests in clinical settings (Wielders *et al.*, 2012). The US Army employed

phase I and II antibody detection, which was initially reported by Bengtson in 1941, to characterize eight outbreaks of Q fever in Allied forces between 1944 and 1945 (Hartzell *et al.*, 2008). For those who are not familiar with Q fever, test results can be misleading because phase I antibodies typically stay high in chronic illness, whereas phase II antibodies are positive in acute illness (Alhethel *et al.*, 2018). The antibody response is a result of phase shifts in *C. burnetii*. IgG titers of 200 or higher against phase II antibodies and an IgM of 50 or higher against phase I antibodies indicate a recent Q fever infection; an IgG titer of 800 or higher against phase I antibodies indicates a chronic infection (Bae *et al.*, 2019). These limitations differ throughout laboratories, and particular limitations for every test must be applied.

Most patients have phase II antibodies within 2 weeks of infection, and 90% of patients have them by 3 weeks (Porter *et al.*, 2011). Antibodies absent after 4 weeks point to a different diagnosis. IgG titers may continue to rise, although antibodies often reach their peak in 2 months and then progressively fall (Wielders *et al.*, 2015). If the elevation continues, a chronic illness (endocarditis) should be suspected.

Clinical endocarditis, isolation of *C. burnetii*, or serological evidence are necessary for the diagnosis of Q fever endocarditis (Cotar *et al.*, 2011). Since Q fever endocarditis is a chronic condition, a single serum specimen suffices for diagnosis; matched sera are not necessary (Psaroulaki *et al.*, 2020). The Duke criteria have been changed to include a phase I IgG titer of 800 or above. An early diagnosis of acute Q fever endocarditis can be made with a positive PCR for *C. burnetii* when there is a high degree of clinical suspicion and the antibody titers are either low or negative (Bae *et al.*, 2021).

The majority of the current guidelines for people with acute Q fever are derived from clinical experience in an elderly population in a single country (El Zein *et al.*, 2024). It's unclear if this kind of care is suitable for all patients. Nonetheless, this method is advised for patients with acute Q fever until research in other populations is completed. While other follow-up techniques could make sense, they should always be used in consultation with an infectious disease expert.

Transmission

Coxiella burnetii is an obligatory intracellular bacteria that is highly contagious to both humans and animals. It possesses resilience and stability in the environment (Celina and Cerný, 2022). In actuality, inhaling infected aerosols can only infect and cause disease in 1–10 healthy individuals (Gregory *et al.*, 2019). Ruminants have been identified as the main source of infection for humans, despite the fact that this agent may replicate in a wide range of animal hosts, including birds, arthropods, domestic mammals, and wild mammals (Robi *et al.*, 2023). These animals mostly transmit infectious agents through vaginal fluids, milk, feces,

urine, and semen when they are infected (Winter *et al.*, 2021). Furthermore, these organisms may endure for a month in chilled meat, 10 months at 15°C–25°C in sheep wool, and 40 months at ambient temperature in powdered milk (Gürtler *et al.*, 2014). The main way that humans become sick is by breathing in contaminated aerosols (Gregory *et al.*, 2019).

When the bacteria infect placental trophoblast cells in the placentas of ruminants and other mammals, they can grow at extremely high densities (Miller *et al.*, 2021). Abortion is a frequently recognized clinical indication in goats and sheep (Winter and Campe, 2022). Mammals either give birth to healthy or sick children when their gestation period ends. At this point, the placenta and birth fluid allow *C. burnetii* spores to enter the environment (de Souza *et al.*, 2022). As a result, *C. burnetii* can pollute the environment and be passed on immediately from birth.

The wind has the ability to spread Q fever up to 18 km from its source (Clark and Magalhães, 2018). The quantity of people afflicted with airborne diseases is also influenced by the intensity of the emission; airborne transmission from source to recipient is contingent upon meteorological conditions, environmental elements, and human exposure (location, duration, and physical activity) (Van Leuken *et al.*, 2016). For instance, the spread of *C. burnetii* is more common in regions with little vegetation and poor soil moisture (Ahmad *et al.*, 2023).

Rarer means of infection include person-to-person transmission, eating unpasteurized milk or milk products, and flea bites (Gale *et al.*, 2015). On the other hand, research on the significance of consuming tainted milk and milk products in the epidemiology of Q fever is still lacking (Pexara *et al.*, 2018). In contrast to aerosol inhalation, higher dosages are thought to be required for a successful infection; nevertheless, the infective dose required for oral transmission of this agent remains unknown. There has been documented epidemiological evidence linking the eating of unpasteurized dairy products to Q fever outbreaks (Mokarizadeh *et al.*, 2023). Furthermore, because of its great heat tolerance and pathogenicity, *C. burnetii* has been regarded since 1957 as the primary microbe that should be removed from milk by exposure to high temperatures (Cho *et al.*, 2023).

Risk factors

Agent factors: The bacterial strain that is causing the infection determines how severe it is. Bacteria of phase I are more pathogenic than those of phase II (van Schaik *et al.*, 2013). The genome of *C. burnetii* type IIII causes acute infections in humans, while types IV and V cause persistent illnesses (Palanisamy *et al.*, 2024). It's unknown how virulent type VI is.

Host factors: Two risk variables that have been shown to affect the likelihood of Q fever in humans are age and gender (Muema *et al.*, 2022). The most susceptible age range is between 30 and 60 years old, and men are

more likely than women to have this clinical illness (Porter *et al.*, 2011). Pregnant women, those with immunosuppressive disorders like AIDS, and those with a history of valvulopathy are the most vulnerable (Robi *et al.*, 2023). Research indicates a comparatively higher incidence in particular occupations, such as veterinary care, laboratory work, slaughterhouse work, and workers with livestock, where there is a higher chance of infection or seropositivity than in other occupations (Cook *et al.*, 2021).

There is a correlation between age and sex and *C. burnetii* infection in animals, particularly in cattle (Mwololo *et al.*, 2022). Numerous studies have demonstrated that in sheep and cattle, the prevalence of *C. burnetii* infection rises with increasing age or parity (Ullah *et al.*, 2019; Nejad *et al.*, 2023). Compared to beef cattle, the frequency is higher in dairy cattle. It is reported that among dairy breeds, Holsteins have a higher incidence (Dhaka *et al.*, 2020). Animal density is a possible risk factor for *C. burnetii* infection because it raises the environmental load of infection (Selim *et al.*, 2023). Numerous studies conducted on cattle indicate that seroprevalence rises as animal size increases (Deressa *et al.*, 2020; Ferrara *et al.*, 2022). Flock size is reported to have a similar effect on sheep (Elsobhy *et al.*, 2021). The seroprevalence of *C. burnetii* infection in animals can also be attributed to a number of management factors, including housing systems and the isolation of new animals (Sadiki *et al.*, 2023).

Seasonal, environmental, and management factors: There are seasonal differences in the incidence of Q fever in people. However, the geographical location affects this variation. Nonetheless, spring or early summer is when the majority of Q fever cases are documented (Halsby *et al.*, 2017). Human Q fever has been demonstrated to be correlated with rainfall rather than seasonality (Van Leuken *et al.*, 2016). Q fever is more common in areas with a high livestock density or around sick animals (Smit *et al.*, 2012).

Public health importance

Q fever is a significant zoonosis that can be dangerous for personnel working in veterinary laboratories, livestock breeding operations, and slaughterhouses due to its high human contagiousness (Plummer *et al.*, 2018). Numerous livestock workers have antibodies, according to surveys, indicating that they were exposed to the pathogen (Dione *et al.*, 2022). The majority of infections are minor, and less than half of those who are infected get sick. However, those who are afflicted may have a high fever along with headaches, aches in the muscles, a sore throat, nausea, vomiting, and pain in the chest and stomach (Sam *et al.*, 2023).

The fever could result in pneumonia or have an impact on the liver and last for a week or two (Honarmand, 2012). The course of treatment entails continuous antibiotic use. A small number of people develop a severe, incapacitating chronic illness. This potentially

catastrophic consequence is more likely to occur in people who already have cardiac valve issues or have weakened immune systems (de Lange *et al.*, 2019). In addition, post-Q fever chronic tiredness syndrome exists (Morroy *et al.*, 2016). The most frequently reported laboratory infection, Q fever, has been known to occur in multiple recorded outbreaks involving 15 or more individuals (Robi *et al.*, 2023).

Initial human exposure to *C. burnetii* can result in acute or chronic disease, as well as moderate or asymptomatic infections (Bauer *et al.*, 2023). Clinical diagnosis might be exceedingly challenging. Even though risk factors for its severity, such as pregnancy, immunosuppression, cardiac valvulopathy, vascular grafts, and aneurysms, have been identified, the causes of this high degree of clinical polymorphism remain largely unclear (Ali *et al.*, 2022). Even with therapy, the condition can be extremely disabling and cause considerable morbidity, even though it is rarely fatal. The majority of cases involving humans are caused by dust particles inhaled from contaminated animals or animal products (Celina and Cerný, 2022).

Potential as bioterrorism

Coxiella burnetii is a biological weapon that can be sprayed on food, water, or even mail. It can also be employed as an aerosol (Stein *et al.*, 2005). Moderate *Coxiella* ingestion is unlikely to result in clinical signs. Human subjects who drank milk tainted with *C. burnetii* experienced seroconversion without experiencing any symptoms of illness (Porter *et al.*, 2011). However, nothing is known about the use of high *Coxiella* concentrations as a food or water product pollutant.

When *Coxiella* is released as an aerosol in heavily populated places, the disease will appear suddenly and resemble a naturally occurring illness (Dragan and Voth, 2020). After the pathogen is released, the outbreak will start 14–26 days later. Individuals will arrive with intense headaches, body aches, and a fever (Honarmand, 2012). Even though the cough may be mild or nonexistent, most patients have radiographic signs of pneumonia (von Ranke *et al.*, 2019). Additionally, some people could have hepatitis symptoms (Jama *et al.*, 2023). It can be difficult to clinically differentiate the initial occurrence from naturally occurring influenza epidemics or from other types of atypical pneumonia, such as mycoplasma or viral pneumonia (Keijmel *et al.*, 2015).

The quick onset of febrile illness epidemics in metropolitan areas with peaks in cases, including exposure to a specific source without secondary transmission, is an epidemiological hint to the employment of Q fever as a biological weapon (Kagawa *et al.*, 2003). It is anticipated that 50 kg of *C. burnetii* would reach an area more than 20 km away and cause around 150 fatalities and 125,000 impairments if it were released 2 km downwind from a population of 500,000 (Stein *et al.*, 2005). In the months that follow, some 9,000 of the acutely afflicted patients might

develop endocarditis (Bozza *et al.*, 2023). The amount of acute and long-term mental health injuries brought on by this agent is hard to measure, although anxiety levels may be higher than with other agents because of concern about serious long-term consequences such as endocarditis and chronic fatigue syndrome (Morroy *et al.*, 2011). Bioterrorism can potentially attack animals. Q fever can result in pandemic abortions in cattle, raising worries about the use of meat and the possibility of human transmission (Saegerman *et al.*, 2022).

Treatment

Treatment in humans: Acute and chronic Q fever are the two types that affect people. Antibiotics work well against this disease's acute form, but as the infection develops into a chronic form, treatment becomes more difficult and the illness frequently returns, which can result in a high death rate (Kersh, 2013). In patients with Q fever, the length of antibiotic treatment was decided by monitoring their serological titers. As soon as a clinical illness appears, antibiotics should be taken because delaying treatment could be counterproductive (Porter *et al.*, 2011). Acute Q fever typically resolves on its own. Nonetheless, prompt diagnosis and treatment with antibiotics can shorten the illness's duration and lessen its severity. The preferred medications for treating Q fever are hydroxychloroquine and doxycycline (Raoult *et al.*, 1999). Most often, these medications are combined. As an alternative course of treatment, other antibiotics such as erythromycin, rifampicin, clarithromycin, and roxithromycin may be utilized (Gikas *et al.*, 2001). Doxycycline 100 mg twice daily for 2–3 weeks is advised for patients with acute Q fever, especially adult patients and non-pregnant women (Kersh, 2013). It is also possible to combine hydroxychloroquine with doxycycline. Phagolysosome pH is raised by the lysosomotropic medication hydroxychloroquine (Rolain *et al.*, 2007). Since *C. burnetii* needs an acidic environment to reproduce, hydroxychloroquine serves as a bacteriostatic by raising the pH of phagolysosomes (Smith *et al.*, 2019). For the treatment of Q fever, cotrimoxazole is safe to use in pregnant women and children under the age of eight (Ford *et al.*, 2014).

In situations of persistent Q fever, antibiotics such as hydroxychloroquine and doxycycline, especially in cases of native and prosthetic valve endocarditis, can be effectively utilized at a dose of 200 mg per day for a lengthy period of 18–24 months (Stahl *et al.*, 2022). When combined with doxycycline, combination therapy is a more effective way to prevent endocarditis than when used alone. Because of their decreased efficacy against *C. burnetii* infections, rifampicin, macrolides, and quinolones are not typically utilized as alternate treatments for this illness (Fullerton *et al.*, 2021). A crucial steroid alternative, methotrexate, is utilized to control vascular inflammation and preserve the ascending aorta and thorax's homeostasis (Yang *et al.*,

2021). Following antibiotic therapy, follow-up care is required, such as routine heart rate and eye reflex tests. Following the usage of antibiotics, some individuals may experience photosensitivity (Robi *et al.*, 2023). In the late stages of chronic Q fever, which are marked by severe heart failure or the development of an abscess on the heart valves, the use of antibiotics is not advised (Ullah *et al.*, 2022). Under these circumstances, heart surgery is advised. It has also been demonstrated that interferon and tumor necrosis factor are useful treatments for persistent Q fever (Andoh *et al.*, 2007). Treatment can be discontinued in situations of chronic infection when the Phase I IgG antibody titer drops by at least four times and follow-up serological response is required (Wiolders *et al.*, 2015). Q fever infections can result in significant rates of morbidity and mortality if left untreated, so people who are more sensitive to them should receive extra care (Kampschreur *et al.*, 2015). Treatment in animals: There is not much information about treating coxiellosis in animals. The effectiveness of medicines in decreasing bacterial shedding and reproductive loss in animals infected with *C. burnetii* requires extensive research. Tetracycline is generally advised for animal therapy; however, because of its decreased bioavailability following oral administration, tetracycline cannot be used in animal feed during pregnancy as a disease control approach at the herd level (Ullah *et al.*, 2022). In order to prevent reproductive injury in animals suffering from chronic coxiellosis, parenteral administration of two injections of long-acting oxytetracycline at a dose of 20 mg/kg 20 days apart may be helpful (Eldin *et al.*, 2017). Nevertheless, oxytetracycline taken orally did not alter the animal's serological status or lessen the amount of bacteria shed through birth fluids (Astobiza *et al.*, 2013). Tetracycline is an effective way to lower the risk of abortion in ruminant animals caused by other diseases like *Chlamydophila abortus* (Gisbert *et al.*, 2024a). Tetracycline should be administered to pregnant animals at intervals of 2–3 weeks starting on the 95th day of pregnancy and continuing until the postpartum period.

Vaccination

Vaccination has been demonstrated to lower the incidence of animal infections, *C. burnetii* shedding, and abortion (Hogerwerf *et al.*, 2011). Those infected groups receive vaccinations due to the outbreak. In addition to offering effective protection against abortion, the inactivated phase I vaccine has been demonstrated to stop germs from shedding into feces, milk, and vaginal mucus (Porter *et al.*, 2011). Animal immunization experiments using inactivated vaccines showed robust and long-lasting antibody responses and showed that vaccination can reduce the organism's excretion (Sam *et al.*, 2023).

Australian regulators approved a formaldehyde-inactivated vaccine derived from a Phase I strain of *C. burnetii* in 1989 (Graves *et al.*, 2022). At this

point, the Phase II vaccine is 100 times more effective against mouse spleen colonization than the phase I vaccine; therefore, the results are approaching those of the Phase I vaccination (Williams-Macdonald *et al.*, 2023). Nonetheless, it has been demonstrated that vaccination works better in nulliparous animals than in parous animals (Long, 2021). Moreover, vaccinations do not totally remove sickness in goats and animals who have already contracted it. The phase I vaccine is more efficacious; however, those who have had seroconversion or been exposed should not receive the vaccination (Gisbert *et al.*, 2024b). It is advisable to vaccinate young animals for several years after vaccination and to choose sero-negative groups or animals.

Coxevac[®], an inactivated *C. burnetii* PhI-vaccine, has been used off-label in sheep for a number of years in Europe, but nothing is known about how it affects sheep immunological response and health. Furthermore, there are differing suggestions regarding the dosages of vaccines for sheep (Böttcher *et al.*, 2022). The immunological response and few adverse effects suggest that Coxevac[®] is a low-risk, safe vaccination for sheep. It is preferable to have extensive, uniform immunization programs with suitable vaccination schedules within the framework of the One Health philosophy (Winter *et al.*, 2021). Because it costs less to administer a vaccination to sheep (1 ml as opposed to 2 ml for goats and 4 ml for cattle), sheep producers may be more receptive (Bauer *et al.*, 2023).

However, as *C. burnetii* is present in practically all domestic and wild ruminant populations globally, efforts have been made to determine how well the Coxevac[®] (inactivated phase I vaccination) works to suppress infection in endemic circumstances. According to several of these studies, if long-term immunization is carried out, Coxevac[®] may be helpful in controlling *C. burnetii* infection (Astobiza *et al.*, 2011). The field experiment opens a path of inquiry into *C. burnetii* control in wildlife and shows that Coxevac[®] may be useful in lowering the amount of *C. burnetii* that deer shed over time (González-Barrio *et al.*, 2017).

Control

Several hygienic precautions should be put in place during an outbreak to lessen the spread of disease to animals. Waste management techniques that have changed include covering, naturally composting, or plowing waste; using lime or calcium cyanide in the manure; and discarding animal abortions and birth products (Ayilara *et al.*, 2020). Cleaning of contaminated locations, including walkways and stable settings, as well as monitoring animal reproduction (Winter *et al.*, 2021). However, it's still unclear whether different control strategies are successful. According to reports, even in the absence of any control measures, the prevalence of *C. burnetii* in affected herds often declines over time (Robi *et al.*, 2023). This could be

because animals are thought to naturally immunize themselves.

Conclusion

Q fever is a zoonotic disease caused by *C. burnetii*. The most common route of transmission of Q fever is via aerosols contaminated with bacteria. Treatment of this disease can be done by administering antibiotics. Several hygienic precautions should be put in place during an outbreak to lessen the spread of disease to animals.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Author's contributions

DKM, ARK, IBM, and MKJK drafted the manuscript. WW, IM, AOA, and SMY revise and edits the manuscripts. NS, RIM, SWP, and KAF took part in preparing and critical checking this manuscript. RR, IF, SW, and SA edit the references. All authors read and approved the final manuscript.

Data availability

All references are open access, so data can be obtained from the online web.

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