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Review Article

Q fever: etiology, diagnosis, and treatment

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Abstract
Any disease or infection that can spread spontaneously from animals to humans or humans to animals is called zoonosis. The origin of more than 60% of human infections is zoonotic diseases. It covers many pathogens, including bacteria, viruses, fungi, protozoa, and parasites. The emergence, distribution, and patterns of zoonoses are significantly influenced by several factors, including climate change, animal movement, agent-related factors, natural factors, and human impacts. Q fever has been neglected as a zoonotic disease in many developing countries. The causative agent of this disease is the bacterium *Coxiella burnetii* (*C. burnetii*), which is resistant to environmental factors such as heat and many disinfectant compounds, resulting in long-term risk of disease for humans and animals. Since the infection is usually asymptomatic, it is mainly undiagnosed in animals until adverse pregnancy outcomes occur in a herd. In humans, infection leads to severe endocarditis and vascular infection in chronic cases. Despite the importance of this disease, limited information is available about the molecular epidemiology and evolution of this pathogen. Genomic studies can also help to investigate the prevalence of this disease. Likewise, the pathogenesis of *C. burnetii* should be examined by molecular studies. Programs of awareness and ensuring the pasteurization of dairy products before human consumption will help prevent many zoonotic diseases, including Q fever.
Keywords: *Coxiella burnetii*, zoonosis, public health, Q fever

Introduction

Q fever was first relayed in 1935 as a febrile unknown origin illness with influenza-like symptoms in abattoir workers in Australia (Derrick, 1937). Also, Nine Mile agent suspected was sequestered from *Dermacentor andersoni* ticks obtained from Nine Mile, Montana, which showed characteristics of the *Rickettsia* and virus (Davis et al., 1938). Also, a patient in Montana caught the disease while handling Q fever-infected specimens shipped from Brisbane (Davis et al., 1938). At first, it was called *Rickettsia burnetii*, but then it was renamed *Coxiella burnetii* (*C. burnetii*) (Philip, 1948). Australian Q fever, Balkan influenza, Nine Mile fever, and abattoir fever are other synonyms for Q fever (Hadush et al., 2016). Today, Q fever is more commonly associated with infection of

human, while *Coxiellosis* is used for animal infections (Agerholm, 2013). Q fever is a zoonotic disease that occurs almost worldwide (Pexara et al., 2018; Genova-Kalou et al., 2021). The causative bacterium is intracellular and has many hosts, including ticks, ruminants, fish, birds, reptiles, and humans (Cutler et al., 2007). Small ruminants are considered reservoirs and transmitters of infection to humans, so recognizing this disease in ruminants is important (Abdel-Moein & Hamza, 2017; Ullah, Jamil, et al., 2019). *C. burnetii* can multiply inside lysosomal vacuoles in phagocytic cells. Also, this bacterium can change lipopolysaccharide (LPS) antigens during infection phase I and II (Mori et al., 2017). It can be seen in two morphological forms, the small cell variant (SCV) is the metabolically inactive form that is a very resistant form of *Coxiella*, and the large cell variant (LCV) is the metabolically active form that is seen in the host cell (Sireci et al., 2021). In accordance with the World Health Organization (WHO), Q fever, Rift Valley fever, and Brucellosis are zoonotic diseases that may be misdiagnosed (Kanouté et al., 2017). This agent causes acute and debilitating diseases in human populations. The US Center for Disease Control and Prevention (CDC) has classified this bacterium as a biological agent of category B (Seo et al., 2016).

Etiology

The agent is a Gram-negative and pleomorphic bacterium with a length of 0.2-0.5 μm from the phylum *Proteobacteria*, class *Gammaproteobacteria*, order *Legionellales*, family *Coxiellaceae*, genus *Coxiella* and species *C. burnetii* (Abnave et al., 2017). The period of incubation in humans is variable (usually 2-4 weeks) depending on the dose of inoculation, antigenic phase, and route of infection. Also, this bacterium has a LPS molecule in its cell wall, which exists in two different antigenic forms, phase-I, and II (Abnave et al., 2017). Phase I has complete LPS, but phase-II has an incomplete LPS molecule without the terminal O-antigen (Kuley et al., 2015; Shapiro et al., 2015). *C. burnetii* can exist in two distinct morphological forms that can be distinguished under the electron microscope, LCV and SCV. LCV is a large, metabolically active bacillus, but the SCV is small, coccoid, and metabolically inactive, impervious to environmental stresses, and able to persist in harsh environments (Schleenvoigt et al., 2015; Hadush et al., 2016). Due to the time-consuming and biohazard potential and the need for biosafety level (BSL-3) laboratories, the propagation and isolation of *C. burnetii* are generally not used. Isolation is essential for the genotypic and phenotypic characterization of *C. burnetii* using multilocus variable tandem repeat analysis (MLVA) and multi-space sequence typing (MST) (Selim & Ali, 2020). This agent can persist outside for a long time and is resistant to environmental stress, but it needs host cells for intracellular replication (Bontje et al., 2016). Nowadays, the methods of laboratory animals, cell culture, and inoculation of embryonated chicken eggs are used for the isolation and propagation of *C. burnetii* (Mertens et al., 2017).

One of the methods of isolation of *C. burnetii* is animal inoculation from samples obtained from infected ticks, feces, vaginal secretions, milk, and the placenta fetal parts. Laboratory animals are used as a sample filtration system, the most common of which are mice and guinea pigs. In this method, 0.5 mL of suspension (1:10) is injected intraperitoneally, body temperature and antibody titer are checked, and serological tests are performed. The results can be confirmed by PCR or microscopy using stained samples from the liver, spleen, and lung. One of the most common symptoms is splenomegaly. These samples are then injected into embryonated eggs or cell culture systems to isolate *C. burnetii* (Gache et al., 2017; Mori et al., 2017).

C. burnetii is considered an intracellular pathogen, so traditional cultures are unsuitable for its growth (Kersh, 2022). Shell vial cell culture is a cell culture system that can isolate obligate or facultative intracellular bacteria such as *C. burnetii* (Raoult et al., 1990). In this system, a suspension of *C. burnetii* is injected into human embryonic lung (HEL) fibroblast cells grown in eggshell vials on 1 cm2 coverslips. These

fibroblasts are mainly used for the isolation and propagation of C. *burnetii* (Maurin & Raoult, 1999). After inoculation, it is centrifuged at 700 × *g* for one hour so that the bacteria adhere correctly to the cells. Three shell vials are used for one inoculation. 3, 10, and 21 days after inoculation, vacuoles of *C. burnetii* can be seen under the microscope. After ten days and using the direct immunofluorescence method (IFA), *C. burnetii* can be identified inside the cells of the eggshell vial. The secondary antibody conjugated to fluorescein isothiocyanate (FITC) along with *C. burnetii* antibodies in the vial are collected and incubated at 37 °C and usually for two months in 5% CO_2, and changing the culture medium and periodic assessment of bacterial growth during incubation is done once a week (Mori et al., 2017; Ullah et al., 2022).

Inoculation of embryonated egg has been traditionally used to isolate *C. burnetii*. In this method, egg yolk is inoculated in a sterile medium for 6-7 days, and after 10-15 days of incubation, the yolk sac is harvested. Evaluation of the *C. burnetii* presence and the bacterial contamination absence examined by microscopic observation of stained smears from the wall of the yolk sac. Uninfected yolk sacs are orange and have a sticky consistency, while infected yolk sacs have a straw-yellow color with white spots (Ullah et al., 2022). Genetic and molecular characteristics of *C. burnetii* can be used for epidemiological investigations of disease outbreaks. Also, investigating the genotypic diversity of a pathogen is used to examine interactions between different types and subspecies of bacteria (Sulyok et al., 2014; Piñero et al., 2015). This information helps to control potential reservoirs involved in the *C. burnetii* life cycle (Ianire et al., 2012). Restriction fragment length polymorphism (RFLP), sequence analysis, and pulsed-field gel electrophoresis (PFGE) techniques are used for the molecular analysis of *C. burnetii* (Sulyok et al., 2014). Also, PCR-based typing techniques, i.e., multispacer sequence typing (MSST) and a multilocus variable number of tandem repeat analysis (MLVA) have high reproducibility and have good discrimination power, and both methods can identify/differentiate up to 36 genotypes of *C. burnetii* provide (Van Leuken et al., 2016; Selim & Ali, 2020).

Transmission

Entry of an infected aerosol is the *C. burnetii* transmission main route. Also, the transmission of infection can occur through the contaminated raw food consumption such as milk, skin or mucous contact with a contaminated product, blood transfusion, and mating (Baziaka et al., 2014; Million & Raoult, 2015; Ullah, El-Adawy, et al., 2019). Ticks are primary in animal disease transmission (Ullah, Jamil, et al., 2019). High amounts of *C. burnetii* can be shed from body secretions such as milk, saliva, feces, urine, parturition secretions, and aborted material, which can dry and cause human contamination through airborne particles (Miceli et al., 2010; Bontje et al., 2016). Q fever human-to-human transmission is rare but may occur through contact with parturient women. Forty species of ticks, mainly from the *Argasidae* and *Ixodidae* families, and some other arthropods that feed on animals can transmit this agent (Miceli et al., 2010; Van Leuken et al., 2016). Transmission of infection through tick bites to humans has not yet been proven. However, ticks can transmit *C. burnetii* transstadially and transovarially to their offspring and act as a potential reservoir. Infected ticks can shed large amounts of *C. burnetii* through their feces and cause animal skin contamination. For this reason, ticks play a crucial role in the environmental spread of *C. burnetii* infection (Sprong et al., 2012; Cong et al., 2015; Seo et al., 2016). *C. burnetii* can be present in various body fluids and tissues such as milk, urine, feces, and parturition secretions; the latter is common in reproductive problems (Khaled et al., 2016). Studies have indicated that one billion of these agents per gram of placenta are shed through the labor secretions of an aborted animal (Hadush et al., 2016). Placentas from sheep and goats that are seropositive for *C. burnetii* but asymptomatic can contain more than 109 per gram of placental tissue, although the presence of just one bacterium is sufficient to cause Q fever infection (Vellema & van den Brom, 2014; Freick

et al., 2017; Hadush et al., 2016; Mori et al., 2017). Q fever cases can occur during any month of the year, but most reported illness cases initiate in the spring and early months of summer, peaking in April and May. This period is also the peak of the cattle, sheep, and goats birthing season (fig. 1) (Maurin M, 2022). *C. burnetii* is periodically shedding in body fluids depending on the host species and shedding methods. Infected cows can shed pathogens in their milk for several months without clinical signs (Lucchese et al., 2015). PCR is used to find out the bacterial load in vaginal and milk samples. 104-108 bacteria during the acute phase of the disease are found in vaginal swabs, while 102-106 bacteria are observed in each milk sample (Sting et al., 2013). Animals of seropositive may not shed the organism. Some healthy animals may shed the organism even if they are seronegative (Saglam & Sahin, 2016; Mori et al., 2017). According to the route of excretion of bacteria from the body, the *C. burnetii* prevalence in milk samples obtained from ruminants may differ. The main routes of shedding bacteria in sheep are through vaginal fluids and feces, while in cows, the primary way of bacterial shedding is through milk. In goats, the organism is excreted through milk, vaginal mucus, and feces (Mohammed et al., 2014; Vellema & van den Brom, 2014).

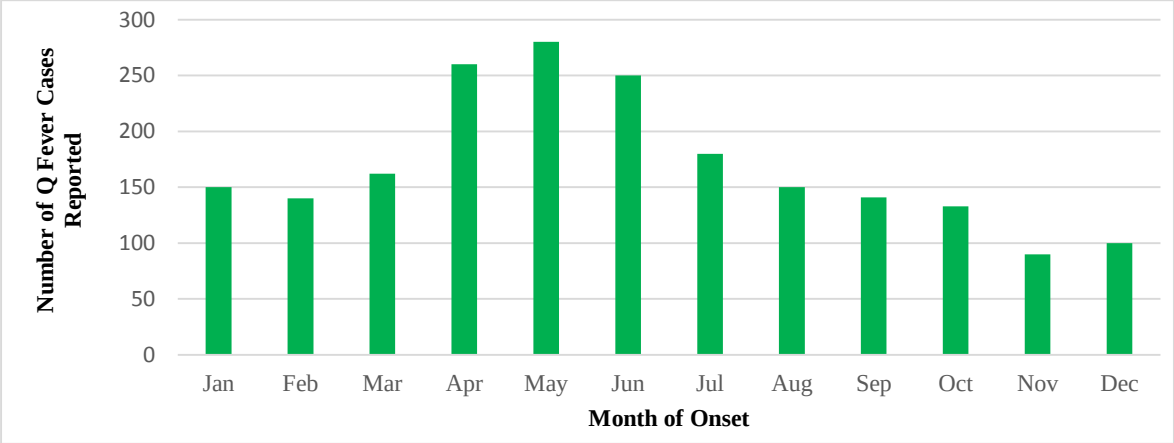

Fig. 1. The Q fever reported cases number by month of onset, United States, 2000–2019.

Pathogenesis

C. burnetii has a distinctive feature called cell wall phase variation. Bacterial phase I has a complete LPS molecule and is very dangerous. This bacteria form can be separated from humans,ticks, and infected animals. Bacteria of phase II can be attained after phase I bacteria serial passages in embryonated eggs cell culture. Phase II has a rough and short LPS, and in addition to LPS, the *C. burnetii* two antigenic forms differ in surface charge, cell density, and surface protein configuration (Shah et al., 2015; Mertens et al., 2017). Morphologically, there are two distinct forms of *C. burnetii*, SCV and LCV. The SCV is the metabolically inactive form that is a very resistant form of *Coxiella*, and the LCV is the metabolically active form that is seen in the host cell. These SCVs are excreted by infected animals, leading to environmental contamination (Selim & Ali, 2020).

Inhalation and consuming contaminated milk and milk products is the *C. burnetii* main transmission route in animals and humans (Woldehiwet, 2004). Once the organism enters the body, it attaches to the monocytes/macrophages cell membrane. This binding is stimulated by the integrin avb3, while

for non-pathogenic bacteria, avb3 and the complement receptor CR3 mediate binding. Phase II bacteria are eliminated inside phagocytic cells, but phase I bacteria persist, and host cells phagocytize phase II bacteria much more than phase I bacteria. Macrophages and monocytes phagocytose SCV, combine with lysosomal contents, change into a metabolically active form, undergo vegetative growth, and finally become LCV. Both *C. burnetii* antigenic forms are ordinarily present in phagolysosomes, but phase II bacteria are rapidly destroyed. Also, the phagolysosomes environment is acidic. It is very favorable for the *C. burnetii* growth and protects it against the effects of various antimicrobials, and finally, this organism can cause a persistent infection. A metabolically active Phase I bacterium's growth cycle occurs in the phagolysosome (Van Schaik et al., 2013; Selim & Ali, 2020). Little information is available about the host cellular immunity role in infections of human. *C. burnetii* infection in goats showed that IgG and IgM phase II antibodies could be detected within two weeks after infection, and their titers were high in blood for up to 13 weeks. Four weeks after forming phase II antibodies, phase I antibodies are detected. The immune response against *C. burnetii* can persist for several months to years, and metabolically active LCV can be detected in placental trophoblasts (Van den Brom et al., 2015). In acute infections, the organism can be detected in the host's blood, liver, spleen, and lungs. In non-pregnant animals, the disease is mainly asymptomatic, while in animals of pregnant, the most important clinical manifestations are abortion, weak offspring, premature birth, and stillbirth. In areas at risk of infection with this agent, there is a correlation between digestive and respiratory problems in apparently healthy children. Although reproductive disorders are not expected *C. burnetii* infection consequences in domestic animals, infection with this agent can increase the abortion rate by up to 90% in goats (Van den Brom et al., 2015; Ullah, Jamil, et al., 2019).

Infection with *C. burnetii* in humans can occur both acutely and chronically. The acute form is often self-limiting with mild flu-like symptoms, but the disease chronic cases are often associated with chronic endocarditis (Chakrabartty et al., 2016). In cases of abortion caused by infection of *C. burnetii*, the embryos usually look fresh and normal, but sometimes the embryo is seen as necrotic. The placenta has inflammation and purulent yellow-brown exudates in the inter-cotyledonary spaces. In the microscopic view, the trophoblastic cells in the inter-cotyledonary area of the allantoic-chorion are mostly affected. Epithelial cells in chorionic membranes usually have basophils and vacuolated cytoplasm. A mild granulation can be observed in the liver (Van den Brom et al., 2012; Van den Brom et al., 2015).

Clinical symptoms in humans

It can result to acute infection in humans, manifesting as pneumonia, mild febrile, and hepatitis. However, in some cases, the disease becomes chronic and causes stillbirth and abortion in pregnant women. It is also the cause of endocarditis. Q fever is considered a self-limiting disease (Polo et al., 2015; Chakrabartty et al., 2016). Approximately 40% of patients show clinical symptoms, but about 60% of infected cases are asymptomatic. Patients with valvular disorders, immunocompromised individuals, and cases of microbial arteritis are more susceptible to this infection (Isken et al., 2013). Q fever more cases are reported in older people. Especially men may be more likely to hold jobs with increased risk for Q fever exposure, such as ranching or livestock management; in accordance with the CDC report, the Q fever risk increases with age (fig. 2) (Maurin M, 2022). The symptoms of the disease are similar to the flu and appear with fever, excessive sweating, restlessness, severe headache, anorexia, upper respiratory tract problems, persistent cough, confusion, chills, and gastrointestinal tract problems such as diarrhea and nausea. Q fever fatigue syndrome (QFS), a debilitating condition following the Q fever acute form, is also seen, occurring in approximately 20% of patients and affecting major body systems. If Q fever turns into

a chronic form, it causes endocarditis. Complications such as pericarditis, myocarditis, nephritis, meningoencephalitis, hemolytic anemia, and retro-orbital pain are chronic Q fever infection rare manifestations (Isken et al., 2013; Van Asseldonk et al., 2013). If the infection occurs during pregnancy, it is usually asymptomatic. However, disorders such as placentitis, abortion, retarded fetal growth, premature birth, stillbirth, and the weak children birth have been relayed (van der Hoek et al., 2011; Vellema & van den Brom, 2014). The morbidity rate of *C. burnetii* infection is high, but the mortality due to it is low, so mortality has been reported in 1-11% of patients with chronic Q fever (Hadush et al., 2016). This agent can also cause serious long-term effects on the patient's health and social life. The economic losses caused by the Dutch Q fever outbreak (2007–2010) were estimated to be 0.307 billion EUR (Van Asseldonk et al., 2013; Van Asseldonk et al., 2015). A recent study in 23 EU member states looked at human cases of Q fever from 2015 to 2019 and reported an average of 0.2 cases per 100,000 people per year (Kersh, 2022).

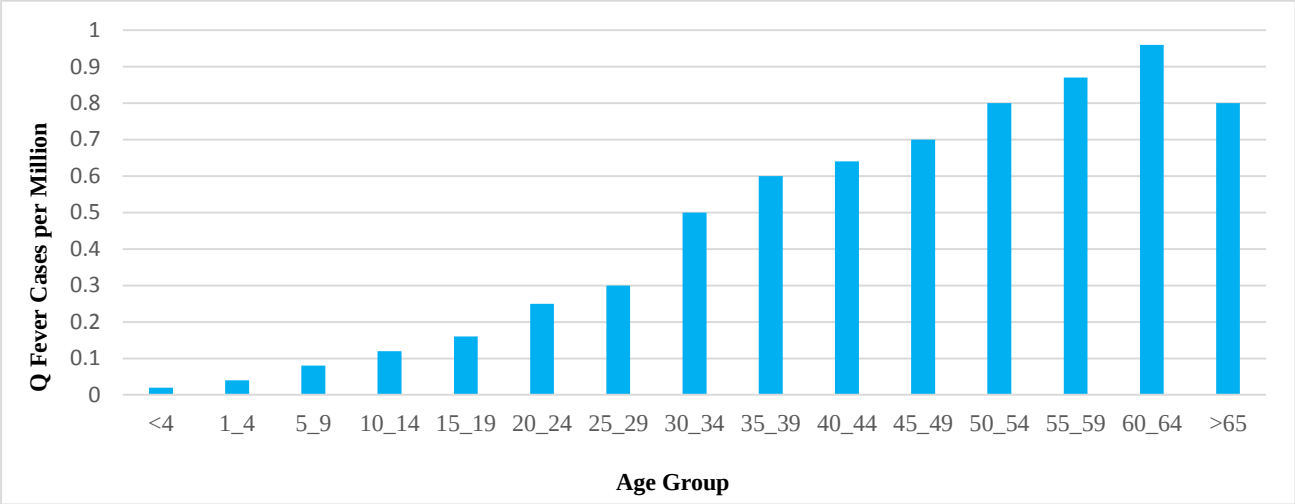

Fig. 2. Reported Q fever average annual incidence (per million population) by age group–United States, 2000-2019.

Clinical symptoms in animals

C. burnetii in animals often occurs without apparent clinical signs. In small ruminants, *C. burnetii* is one of the most cases of abortion. Goats and sheep are the main reservoirs of *C. burnetii* in ruminants. Outbreaks of Q fever in the Netherlands were also linked to infected goat farms near residential areas (Duron et al., 2015; Khaled et al., 2016). *C. burnetii* in small ruminants usually leads to reproductive problems such as abortion in late pregnancy, stillbirth, the weak offspring birth, and premature birth and is also associated with infertility in cattle (Hadush et al., 2016; Freick et al., 2017). Acute *C. burnetii* usually presents as a subclinical infection in cattle, but chronic infection may lead to reproductive disorders (Freick et al., 2017). In sheep and goats, abortion caused by infection of *C. burnetii* is usually between 3 - 8% (Van Asseldonk et al., 2013). The *C. burnetii* recent outbreak in the Netherlands also caused abortions of up to 60% in pregnant goats in the last month of pregnancy. The affected animals had no clinical symptoms, but endometritis was documented in some goats with an abortion history. A decrease in birth weight and respiratory and digestive problems were also seen in offspring

(Ganter, 2015). *C. burnetii* infection in dairy animals can result to subclinical mastitis. This organism lives in the pregnant dairy animal placenta and mammary glands. In small ruminants, the shedding of bacteria through parturition secretions is very high, but in cattle, it is much less (Shapiro et al., 2015; Freick et al., 2017). In a study in Turkey, a total of 832 samples (205 goats and 627 sheep) were obtained from 126 herds**,** total seroprevalence was found to be 13.22%, but the proportion of seropositive herds was 42.85%. The seroprevalences were 14.19% in sheep and 10.24 % in goats. The herd seropositivity rates were 46.31% in sheep and 32.25% for goats. The local seroprevalence varied between 1.38% and 21.79% (Karagul et al., 2019). In a recent study conducted in Ethiopia, the *C. burnetii* individual seropositivity in livestock was 48.8% in goats, 9.6% in cattle, 55.7% in camels, and 28.9% in sheep. In humans, the *C. burnetii* seropositivity was 27.0%, with a prevalence in males of 28.9% vs. 24.2% in females (Ibrahim et al., 2021). In a study conducted in Iran, the *C. burnetii* antibody prevalence in cattle was 13.30%, camels 28.26%, goats 31.97%, sheep 24.66%, and dogs 0.55% (Mohabbati Mobarez et al., 2017).

Diagnosis

Diagnosis of *C. burnetii* based on post-mortem examinations or clinical symptoms is very difficult due to the lack of specific symptoms and disease lesions (Niemczuk et al., 2014). Therefore, laboratory tests are needed for accurate diagnosis. Four diagnostic techniques categories are available for the *C. burnetii*: (i) diagnosis of isolation of the agent, which requires a BSL-3 laboratory using tissue culture, embryonated chicken eggs, or laboratory animals, (ii) Serological tests including Indirect Fluorescent Antibody (IFA), Enzyme Immunoassay (EIA) and Complement fixation test (CFT), (iii) genomic assays such as PCR and (iv) antigen assays such as immunohistochemical staining (IHC) combining laboratory tests such as PCR for nucleic acid detection and ELISA for serology (Niemczuk et al., 2014; Bontje et al., 2016). Both ELISA and IFA methods in ruminants are proper techniques for the Q fever serological investigation, but in humans, IFA is pondered for diagnosing Q fever due to its high sensitivity and specificity (Meekelenkamp et al., 2012; Muleme et al., 2016).

Serological tests

Due to the expensive and laborious nature of isolation techniques and lower sensitivity, serological techniques are preferred to diagnose Q fever. The serology method is used in animals to estimate the infection prevalence and in humans to detect the difference in antibody titer in chronic and acute infection (Lucchese et al., 2015; Saglam & Sahin, 2016). In the chronic form, both IgA and IgG antibody titers against both phases I and II bacteria are high, but in acute infection, only IgG antibody titers against phase II antigens are high (Niemczuk et al., 2014; Shah et al., 2015; Wielders et al., 2015; Van Leuken et al., 2016).

Immunofluorescence assay (IFA)

The immunofluorescence method is a reference method for identifying antibodies of *C. burnetii*. It can follow the disease status in humans and identify patients at chronic infection risk. Suspected Q fever acute and chronic forms can also be detected by measuring antibody titer of phase I, and Phase II is recognizable. If the antibody titer of phase I is higher than the phase II titer, it indicates the Q fever chronic form. The result shows an acute infection if the phase II antibody titer is higher than the phase I titer. If the IgG antibody titer is $\geq$1:800 against phase I antigen, it indicates endocarditis caused by Q fever. Currently, there is no commercial IFA kit for *C. burnetii* in animals, but this method detects Q fever in humans (Herremans et al., 2013; Ferraz et al., 2016; Selim & Ali, 2020). IFA is the gold standard for diagnosing Q fever in humans. However, this method is unsuitable for the early diagnosis of acute Q fever due to the delay in developing an antibody titer (7-15 days after the clinical disease onset). Also, the species-specific IFA cannot be used at the herd level, and for this reason, IFA is not used for the *C. burnetii* infection routine diagnosis in animals (Pan et al., 2013; Selim & Ali, 2020).

Complement Fixation Test (CFT)

The complement fixation test is considered a reference assay for diagnosing Q fever but is useless due to its low sensitivity. Also, anti-complementary activity in several samples prevents the estimation of antibody titers and anti-C. *burnetii* antibodies present in sheep and goats serum samples cannot be regularly detected by IFA antigen (Shapiro et al., 2015; Selim & Ali, 2020).

Enzyme-Linked Immunosorbent Assay (ELISA)

This method is more sensitive and specific then other serological methods and is approved by the European Food Safety Authority (EFSA). In animals, this method is preferred to IFA and CFT due to the ease of screening at the herd level and its ability to detect antibodies of *C. burnetii*, and IDEXX documented 100% sensitivity and specificity of their ELISA kit (Mertens et al., 2017; Ullah, Jamil, et al., 2019; Selim & Ali, 2020). According to studies, ELISA assay using ruminant antigen is more sensitive than tick antigen, so EFSA recommends this method for the ruminants *C. burnetii* antigen. ELISA can detect antibodies against both antigenic *C. burnetii* phases in this method, and the results interpretation is presented as positive, suspected, or seronegative (Ohlson et al., 2014; Selim & Ali, 2020).

Staining

This method examines stained vaginal mucus smears or tissues under a microscope to identify the causative agent. *C. burnetii* is an acid-resistant bacterium. Various stainings such as Stamp, Gimenez, and Machiavelli are the most suitable options, also Giemsa staining, modified Ziehl-Neelsen, and modified Koster staining can also be used. If the result is positive, it is the only possible sign of infection with *C. burnetii*, and other cases should be checked to confirm the diagnosis (Ohlson et al., 2014).

Polymerase chain reaction (PCR)

This method is used for the molecular detection of *C. burnetii*. Its features include high-performance speed, specificity, and high sensitivity to determine and detect the number of bacterial DNA small concentrations, which is significantly used in research and diagnostic methods (Selim & Ali, 2020; Hussain et al., 2022). PCR can be conducted on various biological samples, such as genital swabs, fetal fluids, fetal membranes, or aborted fetuses samples (contents of abomasum, liver, and lung). Blood, serum, urine, milk, throat, and anal swab samples are also helpful for *C. burnetii* genomic detection using PCR (Selim & Ali, 2020; Hussain et al., 2022). Valve material can also be sampled for endocarditis in cases of chronic infections, vascular segments in cases of vasculitis, and bone biopsies in arthritis. Since the antigen is shed alternately in vaginal secretions, milk, urine, and feces, it is better to use sequential sampling for the pathogen genomic detection (Mori et al., 2017; Niemczuk et al., 2014). PCR targets the IS1111 sequence, a *C. burnetii* repetitive transposon-like element that is highly sensitive and specific for genomic detection. However, IS1111 cannot be used for DNA of *C. burnetii* quantification due to multiple copies and misidentification with *Coxiella-like* organisms. Single-copy genes such as icd and com1 help quantify DNA of *C. burnetii*. Different pairs of primers that target different genes such as isocitrate dehydrogenase (ICD), superoxide dismutase (SOD), heat shock proteins including htpA and htpB, as well as macrophage infection enhancing protein (cbmip) can be used to detect DNA of *C. burnetii* (Khalili et al., 2015; Selim & Ali, 2020). The first two weeks after the clinical infection onset is the best time for PCR assays to detect DNA of *C. burnetii* in blood or serum samples. Due to the delay in antibody titer, serological tests are not useful in this period. IgG antibody titers increase two weeks after the clinical symptoms onset, and at the same time, DNA of *C. burnetii* in the blood becomes undetectable. Therefore, after two weeks from the clinical infection onset, serology methods can be used (Niemczuk et al., 2014; Wielders et al., 2015). When animals of seropositive are identified in a herd by serological assays, PCR is the method for tracking the shedders (Niemczuk et al., 2014).

Prevention and Control

Regular surveillance and the implementation of appropriate prevention and control strategies are essential to reduce the spread of the disease, prevent economic losses caused by reproductive

losses, public health, and prevent the potential risk of infection transmission to humans (Ganter, 2015; Meadows et al., 2016; Van Asseldonk et al., 2015). Over time, the prevalence of Q fever decreases even without adopting control strategies, which may be due to the host's natural immunity against this agent (Selim & Ali, 2020). Management points such as vaccination for prevention, covering or purifying manure with lime, wool-cutting management, restricting the free movement of animals, and proper aborted materials burial are essential to consider. Disinfection of calving pens, correct disposal of aborted fetuses, changing the bedding, and disinfection of the umbilical cord are crucial to reducing the disease transmission risk. In order to prevent the further infection spread in the environment, it is necessary to immediately dispose of fetal membranes and dead fetuses in order to prevent eaten by dogs, wild carnivores, and even domestic animals (Shapiro et al., 2015; Van den Brom et al., 2015; Meadows et al., 2016). Conducting quarantine and prohibiting the raw milk consumption from contaminated dairy farms for any purpose because bacterial excretion is quickly done through the milk of infected animals (Lucchese et al., 2015; Hadush et al., 2016).

Education and awareness of people related to livestock are essential in reducing the disease outbreaks risk. People with supervisory roles should wear protective equipment such as masks, gloves, and protective clothing and disinfect sampling materials immediately after use (Ganter, 2015). Transporting animals, especially animals in labor, should be avoided during outbreaks of abortion (Boden et al., 2014; DePuy et al., 2014). Q fever is a zoonotic disease, so interdisciplinary collaboration between livestock farmers, veterinarians, physicians, and laboratories is needed to understand how its agent circulates and to plan for its prevention and control (Bellini et al., 2014).

Vaccination is followed by an active immune response against the potential pathogen (Lacasta et al., 2015). In endemic areas of Q fever, for animals containing Nine Mile RSA 493 *C. burnetii* strain, the use of a phase I inactivated vaccine isolated from ticks is recommended by the OIE, and according to the results, it can reduce the rate of abortion and bacterial shedding (Selim & Ali, 2020). Also, using an inactive vaccine (Coxevac®, Ceva Santé Animale, Libourne, France) in non-infected sheep and goats has led to a reduction in the rate of abortion and bacterial shedding. Using the Coxevac vaccine also reduces bacterial shedding during pregnancy in humans. In 2010, in the Netherlands, a large-scale vaccination with an inactivated phase I vaccine in herds of small ruminants was very effective. After that, no *C. burnetii* abortions were reported from vaccinated herds, and a gradual decrease in these vaccines occurred (Van den Brom et al., 2015). Repeated annual vaccination is recommended in areas at risk in susceptible herds with young animals (Ullah et al., 2022). In Australia, the Q-VAX® vaccine (Seqirus, Parkville, VIC, Australia), a phase I inactivated whole-cell vaccine, is routinely recommended in people occupationally exposed to Q fever infection (Schoffelen et al., 2015)

Treatment in humans

In humans, Q fever can be seen in acute and chronic forms. The duration of treatment is determined according to the patient's serological titers. When there is an acute form of the disease, the use of antibiotics is effective, but when the infection reaches its chronic form, more time is needed for treatment, and as a result, the probability of disease recurrence and mortality is high (Pan et al., 2013; Godinho et al., 2015; Alves et al., 2017). Although this disease is self-limiting, early diagnosis and prescribing of appropriate antibiotics can reduce the infection duration and the symptoms severity. One of the best drugs used is doxycycline at a dose of 100 mg twice a day for 2 to 3 weeks for patients with the acute form of the disease. Another drug is hydroxychloroquine, which is usually used together with doxycycline. Hydroxychloroquine is lysosomotropic and increases the the phagolysosome PH. As a result, it acts as a bacteriostat because *C. burnetii* needs an acidic environment to multiply (Hadush et al., 2016). Other antibiotics, such as erythromycin, clarithromycin, and rifampin, can be used as

alternative treatments (Godinho et al., 2015; Schoffelen et al., 2015; Hadush et al., 2016). In the case of pregnant women and children less than eight years of age, cotrimoxazole can be used to treat Q fever (Shah et al., 2015).

In the chronic form of Q fever, especially valvular endocarditis, antibiotics such as doxycycline and hydroxychloroquine can be combined with a dose of 200 mg per day but for an extended period of 18 to 24 months. The use of macrolides, rifampicin, and quinolones as an alternative treatment for this disease is not recommended (Baziaka et al., 2014; Shah et al., 2015). Methotrexate, a critical steroid compound, can suppress vascular inflammation and maintain hemostasis (Baziaka et al., 2014). In some patients, Photosensitivity occurs after taking antibiotics; also, eye reflex and heart rate examinations are necessary after antibiotic treatment. In the advanced and chronic stages of Q fever, the formation of abscesses in the heart valves and severe heart failure can be seen, in these cases the use of antimicrobial drugs is not desirable and heart surgery is recommended(Shah et al., 2015; Ferraz et al., 2016). In studies, the use of tumor necrosis factor (TNF) and interferon (IFN) has been reported to be effective for the treatment of chronic Q fever (Shah et al., 2015; Hadush et al., 2016). In chronic cases of infection, serological response follow-up should be done, and treatment can be stopped when the IgG antibody titer of phase I has decreased by at least fourfold. In susceptible people with underlying diseases, there is a possibility of death if not treated (Godinho et al., 2015; Chieng et al., 2016).

Treatment in animals

Unfortunately, limited information is available on the treatment of *C. burnetii* in animals, but tetracycline is usually recommended for therapeutic purposes. Despite this, the use of tetracycline in animal feed to control the disease at the herd level has not been effective due to reduced bioavailability after oral consumption. Two injections of oxytetracycline (long-acting) with a dose of 20 mg/kg at an interval of 20 days may help in cases of abortion caused by *C. burnetii* infection. However, using this compound orally did not have a beneficial effect in reducing the shedding of bacteria and altering the serological status of animals (Anderson et al., 2013; Ganter, 2015).

Conclusions

Many infectious diseases are zoonoses, and in addition to animals, they pose a significant risk to human health. Increasing contact between people and wild animals, climate change, environmentally undesirable human activities, and changing food habits affect the emergence and re-emergence of zoonotic diseases. Q fever is neglected as a zoonotic disease in many developing countries. *C. burnetii*, which is the cause of this disease, can survive for a long time in harsh environmental conditions. Human health can be threatened through asymptomatic animal infections and endanger public health. Pathobiological studies, including epidemiology, genomic information, and host-pathogen relationships, can help to understand how pathogens spread and evolutionary relationships. Protective measures such as ensuring that milk is pasteurized before consumption and regarding hygiene issues when working with animals can prevent human infection. According to studies, the prevention and management of this disease require more attention and care from veterinarians and physicians, and organizations related to the health of animals as well as human societies, and it proves the need to hold training courses in this field and the need to provide modern diagnostic facilities in animal and human hospital centers.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

Ethical approval

Not applicable.

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