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Coxiella burnetii, A Neglected Infectious Bacterium of Global Distribution

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Abstract

COXIELLA burnetii is an obligate intracellular bacterium of worldwide distribution, which results in a highly infectious zoonotic disease known as Q fever or coxiellosis in a wide range scale of hosts including domestic and wild ruminants, birds, murine animals, and arthropods as well as humans. Among domestic ruminants, cattle, sheep and goats are the major reservoirs for the pathogen; and frequently, human outbreaks of Q fever are related to domestic animals. Under farm conditions, *C. burnetii* is extremely resistant to environmental conditions, and this ability to withstand harsh conditions explains its potential capability to cause severe disease in human and to be deemed as one of the biological terrorist agent. Uterus and mammary glands are the primary sites of infection, particularly in chronic phase, and the shedding of *C. burnetii* to environment occurs mainly by birth products during parturition, milk, urine, faeces, semen, and inhalation. In recent years, *C. burnetii* appears to be endemic in several countries worldwide resulting in severe economic losses in animals and extensive health impacts in human. Therefore, further investigations in the field of human and different animals are highly recommended to providing additional recent information about the extension of *C. burnetii*, and the role of the pathogen in different infections in both domestic and wild animals and humans to develop new active schedules for control and preventing its spreading.

Keywords: Q fever, Coxiellosis, Biological terrorist agent, Rickettsial infections.

History

Although, the cases of unheard-of disease were noticed since the 1930s; the national Australian and American laboratories were worked independently and nearly simultaneously to unveil the aetiology of unknown human infections in Australia and the pathogenic agent isolated from tick in USA in 1935 [1]. In 1935, Raphael Cilento showed that there is an outbreak of undiagnosed febrile illness among abattoir workers in Brisbane (Queensland, Australia), and he learned that cases of the disease had been occurring periodically since 1933 and that additional cases are still reported. Cilento contacted by Dr. Edward Holbrook Derrick and charged him to investigate the situation and determining its cause [2, 3]. Dr. Derrick begun the first actual investigation among abattoir workers and found that the type of fever among most cases is resembled in general way as continued for one of seven to twenty-four days, and most outstanding feature was the uniform failure of blood cultures and agglutination tests to throw light on the diagnosis. Initially, Dr. Derrick suggested that the disease might be typhus, undulant fever, aberrant typhoid or paratyphoid, leptospirosis, in addition to the most common animal diseases, but the results were negatives. Then, the suspicion arose and gradually grew that the type of fever is not described previously and suggested the name of ''Q'', for ''Query'' not for Queensland, fever to denote it until fuller knowledge allows to a better name [4]. Furthermore investigation to isolate the etiologic agent by repeated injection of blood or urine of abattoir patients into guinea pigs was unsuccessful. Unfortunate failure to visualize the pathogen in guinea pig tissues and to cultivate it in various bacteriologic media surmised to a preliminary but erroneously conclusion that the

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etiologic agent is a virus. In October 1936, Derrick sent a saline emulsion of infected guinea pig liver to Dr. Macfarlane Burnet for additional study [5].

Researchers in the Rocky Mountain Laboratory (RML) in Hamilton, USA, were work on a number of RM spotted fever (RMSF)-related projects in 1935, including the disease's ecology and the creation of a vaccine. During that period, 200 *Dermacentor andersoni* ticks were collected from the Nine Mile Creek region in Montana, USA, and sent to Dr. Gordon Davis [6]. The filter-passing infectious agent that Davis extracted from these ticks is thought to be the same as the filter-passing virus that Noguchi described in 1926 and is thought to be *Rickettsia rickettsii*, the etiologic agent of RMSF [7, 8]. Davis states that this bacterium is not the source of tularemia due to the lack of growth on a range of bacteriologic medium and the typical clinical signs seen in experimental animals [9].

In 1936, Dr. Macfarlane Burnet (Australia) began their experimental investigation to detect the pathogenicity of pathogenic agent using the laboratory animals (guinea pig, monkey, mice, and albino rat) and embryonated chicken egg (ECEs). Dr. Burnet summarized that the virus is filterable, and can produce a pathogenic effect and histological changes on guinea pig, monkey and mice but in albino rats [10]. These findings provided the final evidence to that the etiological agent of Q fever is Rickettsia [11]. In USA, Dr. Herald Cox works with Dr. Davis for identification and further characterization of the "Nine Mile Agent". Davis and Cox discovered that the organism had properties of both viruses and Rickettsia as there no inclusion bodies were found in stained preparations of inflammatory cells except numerous, minute, and pleomorphic rickettsial-like organisms were observed. Based on these findings, Davis and Cox summarized quit simply that ''the infectious agent is not a filterable virus [8].

In 1937, Dr. Burnet (Australia) recorded that the agent of Q fever is RickettsiAl, and suggested that the vector is ticks. In USA, Dr. Parker demonstrated that ticks can transmit of Q fever agent actively to guinea pigs by the nymphs and adults ingested previously a contaminated blood, and confirmed that the organism can transfer by the progeny of infected females [12]. In 1938, Derrick (Australia) postulated that there may be one or more species of and domestic animals act as a natural reservoir [5, 13]. In USA, Dr. Dyer revealed successfully that the Australian Q fever agent is identical to the American Nine Mile strain [14]. In 1939, Cox suggested *Rickettsia diaporica* as a name for the pathogen [15]. Since 1939, Dr. Cornelius Philip have performed many experiments concerned with transmission of the Q fever agent which detected that mosquitoes does not transmissible for *C. burnetii*; faeces of infected ticks were very rich by agent; animals become infected when powdered feces of infected tick were dusted in the nostrils, eyes, and mouth in separate tests; pathogenic agent remain highly virulent even stored in at 2.22ºC for 65-127days; and finally, houseflies can be infected when fed on moistened infectious tick faeces [16]. In 1948, Philip proposed to the name of *Coxiella* to as the genus name and *Coxiella burnetii* to Q fever agent (Coxiella referred to Dr. Cox and burnetii to Dr. Burnet [17]. In 1948, *Rickettsia burnetii* isolated for first time from raw milk samples of dairy cows in southern California, demonstrating another potential source of infection [18].

Classification

Initially, the pathogenic agent of Q fever is classified under *Rickettsia* genus of *Rickettsieae* tribe due to its microbiological characteristics [5, 15]. In 1948, Philip proposed that this agent should be placed in a separate new genus named as *Coxiella* of *Rickettsiaceae* family because *C. burnetii* did not behave exactly like atypical *Rickettsia* in addition to its ability to withstand greater exposure to physical and chemical agents than observed for *Rickettsia* [17]. Based on *16S rRNA* gene sequence, *C. burnetii* was reclassified (Table 1), [19].

Bacteriology

Phenotype

Coxiella burnetii is a highly pleomorphic, obligatory intracellular coccobacillus bacterium that is around 0.2–0.4 m in diameter and 0.4–1.0 m in length [20]'. When an organism is subjected to Gram-staining, a great deal of diversity has been seen; nevertheless, electron microscopy has shown that the bacterium's outer membrane has traits common to Gram-negative bacteria, despite the fact that the Gram method typically cannot stain it [21].

Morphology

In 1959, antigenic variability of *C. burnetii* was suggested for first time by Dr. Nonna Kordova [22]. Based on the electron microscopic investigations, McCaul and Williams [23] detected that the developmental cycle having two vegetative forms are the small-cell variants (SCV) and large-cell variant (LCV), in addition to a sporogenic form named spore-like variant (SLV). In 1994, Dr. McCaul demonstrated that *C. burnetii* undergoes another cell variant as identified as an endogenous spore-like-phase (SLP) that formed due to particular conditions [24]. These variants (SCV, LCV and SLV) are differed in their morphologic, antigenic, and metabolic characteristics as well as in physical and chemical resistance [25].

Phase's variation

As observed in pathogenic Gram-negative bacteria as *Brucella* spp. and Enterobacteriaceae, *C. burnetii* displays an antigenic variation from the

smooth to rough form called as the phase-I and the other that shifts from rough to rough mutant form or phase-II [26]. However, Phase-I expresses the full length smooth LPS, contains O-antigen and being virulent; whereas, the phase-II carries the rough LPS, and being avirulent corresponds to lack of O-antigen [26-28]. In addition to galactosamine uronyl-α-(1,6)-glucosamine residues, O-antigens of *C. burnetii* have unusual sugars such as L-virenose and dihydrohydroxy-streptose that do not found in any other enterobacterial LPSs and thus are unique biomarkers [29]. However, the virulent phase-I, which isolated only from the natural sources, can survive and replicate inside the monocytes and macrophages of host in contrary to avirulent phase-II that unable to replicate [30]. In laboratory, the phase-I form undergoes a transition to avirulent phase-II form after several passages in SPF-ECE and tissue culture [31]. Hence, avirulent form cannot be existed in natural environment [32].

Genetic properties

General feature of the genome

The genome of the American Nine Mile strain '(QPH1 plasmid) was partly sequenced in the 1994s [33] and fully sequenced in the 2003s, despite the fact that several genetic investigations have been conducted on *C. burnetii* [34]. According to Seshadri *et al*. [34], *C. burnetii* has a circular chromosomal topology with a genomic size of 1, 9995, 275bp; and encodes 2,134 coding sequences (CDSs), 719 (33.7%) of which are hypothetical. These results showed that this organism is far from the proteobacterial Rickettsia group and any other lineage within proteobacterial subgroup. However, *C. burnetii* is most closely related to the intracellular-arthropod pathogen *Rickettsiella grylli* and the facultative-human pathogen *Legionella pneumophila* [34-36].

Insertion sequences (ISs)

Since there is little probability of gene transfer, ISs are often uncommon in obligatory intracellular bacteria that have few or no ISs. In actuality, these creatures' genomes have limited genomic flux or plasticity, making them comparatively immobile [37]. A highly-conserved IS110-like region of around 1450bp was therefore found in 19 copies in Coxiella's NM strain, known as IS1111, during the initial genome research [Hoover *et al*., 1992]. After the genome sequencing was finished, Seshadri *et al*. [34] came to the conclusion that *C. burnetii* has three defective transposase genes of unknown ancestry and 29 ISs that are distributed across the chromosome but not on the plasmid. According to Denison *et al*. [38], the IS1111 element in *C. burnetii*, which is identified by the inner inverted repeats (IRs), raises transposase expression, while the outer IRs serve as a recognition site for the IS element's insertion.

The genome of *C. burnetii* contains at least 20 copies of the htpAB-associated repetitive element, which is often utilized to identify the organism in clinical and culture samples of acute and chronic infections [39, 40]. Acute and chronic infections have been shown to be caused by 21 strains of *C. burnetii* that have the 27-kDa outer membrane protein linked to pathogenesis and immunity [41]. The *prfB* gene, which encodes peptide chain release factors, the *CpeA-CpeF* gene, which encodes Coxiella's plasmids, the *mucZ* (*dj1A*) gene, which mediates capsule production, the *sodB* gene, which encodes metal ion binding, the qrsA sensor-like protein, and others are all found in *C. burnetii* (Figure 1) [42].

Plasmids

Raoult *et al*. [43] has been shown that most *C. burnetii* isolates harbor 1 of 4 autonomously replicating plasmids termed QpH1 (36kb), QpRS (39kb), QpDV (33kb), and QpDG (42kb); in addition to one plasmid without designation. However, some *C. burnetii* strains appear plasmidless, and carry a large plasmid-homologous sequence integrated into the chromosome [44]. The first detection of these plasmids were as following; (I) QpH1 in the Nine Mile tick isolates [45], (II) QpRS in goat isolate [Samuel *et al.*, 1985], (III) QpDV in French and Russian isolates [33, 46], and (IV) QpDG from feral rodents near Dugway, Utah [47]'. Another not-well-characterized plasmid is derived from a Chinese *C. burnetii* isolates [48, 49].

Epidemiology

Geographical distribution

To investigate the association between human and animals' infections, several surveys have been performed using different types of serological assays, which demonstrated that *C. burnetii* exists among all parts of the world except the Antarctica and New Zealand [50]. In Africa, *C. burnetii* has been largely been underestimated [51]. However, the positive infections were 8-100% in South Africa [52], 39% in Zimbabwe [53], 3.6% in Senegal [54], 31.3% in Cameroon [55], 31.6% in Ethiopia [56], 14.8% in Togo [57], 28.3% in Kenya [58], 14.5-57.1% in Nigeria [59], 4.2% in Algeria [60], 29.92% in Sudan [61], 13.2-40.7% in Egypt [62], 21.7% in Ghana [63], and 6% in Chad [50].

In Asia, seropositive data were revealed on 8.4% in Pakistan [64], 58-60.4% in Japan [65], 25.6% in South Korea [66], 16.3% in Turkey [67], 28.9% in Saudi Arabia [68], 33% in China [69], 3.75% in Bangladesh [70], 4.6% in Thailand [71], 70.9% in Jordan [72], 15.09-30.63% in Lebanon [73], 33.3% in Iran [74], and 19.63% in Iraq [75].

In Europe, *C. burnetii* reported as positivity as 8-32% in Czech [76], 7.8% in Germany [77], 44.9% in Italy [78], 24% in Cyprus [79], 8.53% in Bulgaria

[80], 7.9% in Albania [81], 59% in Denmark [82], 48.4% in Ireland [83], 4.9-46.3% in Greece [84], 16% in Netherland [85], 12.3% in Spain [86], 38% in Hungary [87], and 11.83% in Poland [88].

In Australia, North and South Americas; the positive prevalence showed 25% in Colombia [89], 32% in Brazil [90], 24% in Canada [91], 28% in Mexico [92], 1-73% in USA [93], 0.61% in Australia [94], 12.6% in Ecuador [95].

Host distribution

Numerous hosts have been identified as either reservoirs or vectors that contribute to the spread of illness from one animal to another or even from one species to a person. The first vector of 'Q fever to be discovered simultaneously in Australia and the United States was the tick. Numerous studies have since revealed that *C. burnetii* can infect a wide range of hosts, including pigs [96], dogs [97], camels [98], buffalo [62], mites [99], rabbits [100], domestic and wild birds [65], flies [101], rodents [102], cats [103], deer [104], horses [105], pigs [96], dogs [97], and rabbits [100]. The most prevalent and significant human infection reservoirs are cattle, sheep, and goats [50].

Transmission and source of infection

Because of pseudosporulation process, *C. burnetii* may infect a wide variety of hosts and survive in surroundings for extended periods of time [106]. The most common reservoirs for the spread of infections and human epidemics are cattle, sheep, and goats, since the bacterium is easily eliminated from the feces, milk, urine, and uterine discharges of afflicted animals (Figure 2). Numerous investigations have shown that *C. burnetii* may be found in extremely large quantities in the placenta, foetus membranes, and amniotic fluid of domestic animals that give birth [107]. Furthermore, long after miscarriage, infected animals may likely continue to shed infectious particles [108]. According to Kersh *et al*. [109], the organism may last for extended periods of time in the environment. Aerosols can spread the disease for up to two weeks, and contaminated soil can harbour the organism for up to five months.

Coxiella burnetii may spread by a variety of inanimate things (fomites), such as wool, shoes, clothes, straws, and other materials tainted with animal faeces [110]. According to Nusinovici *et al*. [111], the entrance of sick animals and aerosolized spore-like forms carried by the wind are the primary ways that organisms are introduced to a farm. The most common ways for animals to get infected are by consumption of contaminated pastures and inhalation of organisms from diseased animals and the environment [112].

According to Reeves *et al*. [113], ticks and other arthropods have been linked to domestic animal infections. The epizootic cycle of *C. burnetii* is distinguished from the majority of vector-borne diseases by the lack of any vector specificity [114]. Only 14 hard tick species and 1 soft tick species were recovered from cattle, despite the fact that this bacterium was isolated from over 40 hard tick species, at least 14 soft tick species, bed bugs, flies, and mites [114, 115].

According to Anderson *et al*. [116], chronically infected cows are the most significant source of human infection since they may release varying levels of the organism in their milk and birth secretions over the course of many years. Maximum shedding in cattle occurs after parturition and for up to two weeks later [117]. Unlike ewes that only excrete the organism in their milk for a brief period of time, infected dairy cows excrete *Coxiella* in their milk for many months [118]. The presence of viable organisms in bull semen, which suggests the possibility of sexual transmission of infection during insemination, confirmed that sexual route was also described as a method of transmission among many domestic and laboratory animals as well as humans [119].

Zoonotic aspects

Since they are vital providers of meat, milk and other dairy products, clothing, agricultural fertilizer, and animal traction, domestic cattle have been an integral part of human culture for ages [120]. Since cattle are often a significant source of food security, this function remains crucial in the lives of those who are most economically disadvantaged [121]. Without a public health framework, recent urbanization, population growth, and income increases have led to the rapid expansion and transformation of livestock production in many developing nations, increasing the risk of zoonotic diseases endangering public health [122].

Bovine zoonotic illnesses are more likely to be transmitted by people groups who are more exposed to cattle and cow products [123]. These groups include people who handle livestock, veterinarians, abattoir workers, meat inspectors, laboratory personnel who handle biological samples from infected cattle (such as urine or placental fluid), and people who eat improperly prepared meats and unpasteurized milk [124, 125]. *Coxiella burnetii* was one of the most destructive farm animal-derived zoonotic bacteria in recent decades, especially in the Netherlands, where there were many outbreaks between 2007 and 2010 [126]. Clinical polymorphism is the primary feature of both acute and chronic human *C. burnetii* infections [127].

In its acute phase, which is asymptomatic in about 60% of cases, it is a self-limiting sickness that has a lengthy course and is characterized by fever, weakness, headaches, and a minor illness that resembles influenza. Additionally, a number of chronic consequences are evident, including

reproductive issues, endocarditis, myocarditis, hepatitis, and pneumonia [128]. Transplacental infection, spontaneous miscarriage, intrauterine growth retardation, intrauterine mortality, and preterm delivery are all possible outcomes of organisms in pregnant women [129, 130]. Furthermore, using organisms against soldiers might result in a manpower loss of between 23% and 77%, as well as a significant reduction in operational efficiency [131]. Acute infection fatality rates, however, are estimated to be between 1% and 2% [128, 132].

Chronic infections, such as endocarditis, which is reported in 60–70% of cases, chronic hepatitis, chronic fatigue syndrome, interstitial lung disease [132], osteomyelitis [133], septic arthritis [134], aneurysm and vascular graft infections [135], and spontaneous abortion in pregnant women [136] are the main clinical signs of the chronic form, which lasts for more than six months and affects 5% of infected individuals. Neurological problems [137], pericarditis and lymphadenopathy [132, 138], and ocular neuritis [139] are further uncommon clinical symptoms. According to Watanabe and Takahashi [140], the prognosis for chronic infections is worse than for acute infections because antibiotics are less successful in treating them, and fatality rates might exceed 50%.

Safety issues

According to Jones *et al*. [141], *C. burnetii* is regarded as one of the most biologically dangerous agents because of its great transmissibility and very low infectious dosage, which has been recorded as one bacterium for both humans and guinea pigs. The Centers for Disease Control and Prevention (CDC) in the United States have classified this bacterium as a category B bioterrorism agent [142]. Because of its widespread availability, natural ability to be aerosolized and spread effectively, environmental stability, and capacity to produce large amounts of infectious material that remains viable for years, *C. burnetii* may be a better candidate for use as a biological weapon than category A agents [143]. Russia began producing *C. burnetii* biological weapons in 1940 and continued to do so until at least the early 1990s [144]. Although it has been hypothesized that the USA is manufacturing bombs carrying *C. burnetii*, the biological weapons program was halted by presidential order in 1969–1970 [145].

Pathogenesis

In animals, *C. burnetii* infection is usually acquired via inhalation, ingestion, and arthropod-borne carriage. After first entry, the primary site for localization and multiplication of organism is the regional lymph nodes [146]. Then, hematogenous spread results in re-localization of pathogen, chiefly, in mammary glands and placenta; and rarely, in lung, reproductive tract, bone marrow, liver, spleen and other organs [147]. Elliott *et al.* [148] thought that any nucleated cells can be infected, but the monocytes / macrophages are of major prefers target for *C. burnetii*. *C. burnetii* may be internalized and transported along the classical endosomal route, which ends in an acidic lysosome-like compartment, by means of two mechanisms: active phagocytosis and passive binding to leukocyte response integrin (v×3 integrin) and CR3 receptor [149]. However, since Phase-I attachment is mediated by integrin alone, whereas Phase-II attachment is mediated by both integrin and complement receptor CR3, the internalization route differs for the virulent and avirulent Phase-I and II forms [150, 151].

With the exception of monocytes and macrophages that eliminated Phase-II bacteria, both phases proliferate in the cells after internalization [43]. The capacity to proliferation and expanding within phagolysosomes as well as establishing of chronic infection is crucial [152]. Phagocytosis results in the creation of a phagosome, which then develops into a phagolysosome after a sequence of highly regulated fusion and fission events [153]. As the nascent phagosome matures into an early phagosome, it picks up the small GTPase RAB5, which promotes fusion with early endosomes and causes the lumen to become acidic to around pH 5.4. It also picks up the early endosomal marker protein (EEA1) [43].

Eventually, the many internal phagolysosomes unite to create a sizable, distinct vacuole known as the *C. burnetii*-containing vacuole (CCV) [151]. The formation of Coxiella's intracellular niche, known as the parasitophorous vacuole (PV), occurs after lysosomal maturation and takes around 24 to 48 hours to complete. For days, the organism keeps growing in this PV, creating a big vacuole that may fill most of the cytoplasm of the host cell and hold up to 100 bacteria each [154, 155]. By making tight contact with the early endosome membrane, SCV internalizes monocytes and macrophages. Within the first hour, its Type IV secretion system (T4SS) starts introducing effector proteins into the cytoplasm of the host cell. About eight hours after internalization, SCV changes once the vacuole becomes acidified, and the resultant LCV is then replicated. On the second day, the PV is roomy and has the repeating LCV. Around day 6 (the start of the stationary phase) after a few days of replication (long-phase growth), SCVs start to resurface. About 50% of the Coxiella in a PV are SCVs on day 8. On day 12, there are a lot of SCVs in the PV. The cycle is then repeated when PV is lysed by an unidentified mechanism, releasing SCVs [156, 157].

Immunology

The interaction between *Coxiella* and the host immune system is complex and remains inadequately understood [43]. The presence of *C. burnetii*-specific

antigens on the membranes of infected host cells supports the hypothesis that these cells are recognized by the immune system and subsequently lysed through antibody-dependent cellular cytotoxicity (ADCC) involving monocytes, macrophages, and other cells [158]. The effective clearance of *C. burnetii* is associated with the activation of both innate immune pathways and subsequent adaptive immune responses [159].

Innate immunity

Coxiella burnetii persists in resting monocytes without replication, inducing an M1-type program typically activated by IFN-γ or bacterial products, thereby enhancing microbicidal activity [160]. *C. burnetii* replicates in macrophages and induces the expression of genes associated with the M1 program, as well as M2 polarization-related genes encoding transforming growth factor [161]. The polarization of macrophages into M1 or M2 phenotypes regulates the intracellular lifecycle of *C. burnetii* [162]. Phase I *C. burnetii* has been shown to infect and replicate within dendritic cells without prompting maturation or the production of inflammatory cytokines [163]. Additionally, the role of natural killer cells in *C. burnetii* infection is not well elucidated [164]. Elliott *et al*. [165] demonstrated that *C. burnetii* delays neutrophil recruitment for approximately seven days.

Adaptive immunity

Multiple lines of evidence from both animal models and clinical studies establish that adaptive immunity is necessary for protection against *C. burnetii* infection [166]. Faugaret *et al*. [161] noted that effective management of acute *C. burnetii* infection depends on a systemic T-cell response characterized by Th1-type activity, granuloma formation, and the production of INF. Schoffelen *et al*. [167] experimentally demonstrated that INF-γ stimulates the microbiocidal program against *C. burnetii*, restores phagosome-lysosome fusion, and influences phagosomal pH. Clemente *et al*. [159] found that INF-γ promotes the apoptosis of Coxiella-infected macrophages in a manner dependent on tumor necrosis factor (TNF), as INF-γ up-regulates TNF production and induces the expression of TNF on the membrane. In the context of chronic infection, granuloma formation is infrequent, being supplanted by lymphocyte infiltration and areas of necrosis in the liver [168]. Antibodies that emerge 3-4 weeks post-onset of clinical symptoms in primary *C. burnetii* infection are deemed non-essential [169]. The majority of anti-Phase II antibodies are associated with low levels of anti-Phase I antibodies during acute infection; conversely, in the chronic stage, there is a higher titer of antibodies against the Phase I antigen [170, 171]'. Andoh *et al*. [172] noted that elevated levels of specific *C. burnetii* antibodies during Phase I and Phase II hold diagnostic significance, as these antibodies contribute to the regulation of the infection, irrespective of their impact on bacterial clearance.

Clinical signs

Coxiella burnetii exhibits high infectivity, with a minimal infectious dose of one organism; however, the clinical progression of the disease is significantly influenced by host characteristics and the route of inoculation [157]. The natural reservoir of organisms includes various 'free-living vertebrates; however, the primary risk for human infection is associated with contact with infected ruminant livestock and their contaminated products [173]. In animals, infection with *C. burnetii* is often asymptomatic or subclinical [174]. Multiple studies indicate that parenteral inoculation of *C. burnetii* in calves may lead to transient pyrexia and, in some cases, mild respiratory disease [175]. Barlow *et al*. [176] demonstrated that extensive inoculation of organisms can lead to localized proliferative infections, resulting in acute, short-lived mastitis and a concurrent systemic response. *Coxiella burnetii* was found to persist in various tissues beyond the mammary gland, including bone marrow, heart valve, intestine, liver, lung, and uterus [147]. Both experimental and natural infections in pregnant animals have demonstrated the strong affinity of *C. burnetii* for ruminant placenta [177, 178]. Consequently, elevated levels of infectious organisms may be discharged during parturition, leading to significant environmental contamination [109]. The outcome of *C. burnetii* infection in pregnant animals can result in various conditions, with the complexity of events contributing to both normal and abnormal outcomes [179].

Laboratory testing

Given the nonspecific or absent clinical symptoms and lesions associated with *C. burnetii*, laboratory testing remains the sole reliable method for confirming the presence of the pathogen [108]. Various assays have been outlined for diagnosing *C. burnetii* in animals, encompassing both direct organism identification and serological methods.

Direct identification of C. burnetii

Staining

Gimenez, Stamp-Macchiavello (Macc), modified Ziehl-Neelsen, and modified Koster are the most available staining techniques used to visualize *C. burnetii* on smears or frozen tissue from placenta of aborted ruminants or other body tissue, from the fetus stomach content, and from vaginal discharge [180, 181]. These tests have low diagnostic sensitivities and specificities, and required more attention because *C. burnetii* can be confused with *Chlamydophila abortus* or *Brucella* spp. [182, 183].

Immunohistochemistry (IHC)

Immunodetection can be achieved for detection of chronic *C. burnetii* in fresh samples or after formalin/acetone fixation and paraffin embedding smears [21, 184]. In this method, *C. burnetii* IgG-antibodies is labelled with either Fluorescein isothiocyanate (FITC) or preoxidase assay to conjugate and visualize of pathogen in tissues [183, 185]. IHC is one of the most important and commercially available diagnostic methods which applied widely to confirm the diagnosis of *C. burnetii* infections in foetuses and placenta tissues of cattle [186], sheep [187] and goat [188], as well as in valvular and vascular samples of human [189].

Bacterial culture (Isolation)

In vitro, cell culture of organism remains the gold standard for diagnosis of bacterial infections. *Coxiella burnetii* can culture efficiently in SPF-ECE, laboratory animals, and in many tissue using different specimens such as milk, vaginal swabs, faeces, and placenta [183]. Nonetheless, cultivation of *C. burnetii* stills technically difficult process, rarely performed due to the human health risk, fastidious to growth, required to Biosafety-Level 3 laboratory and for high levels of organism to be reliably cultured [190]. As a result, culturing of *C. burnetii* is not practical in epidemiological studies, and rarely performed particularly in veterinary medicine [173, 191]. In 2009, a citrate buffer-based medium termed complex *Coxiella* medium (CCM) was developed, which provided an amenable axenic (host cell free) culture allows for prolonged and optimal metabolic activity of organism, and had little effect on metabolism [192].

Molecular assays

Polymerase chain reaction (PCR) is a widely utilized molecular diagnostic method that amplifies a target sequence in a tested sample using synthetic primers. The availability of primers derived from genes specific to *C. burnetii* has facilitated a simple and reliable tool for detection. PCR has demonstrated greater sensitivity compared to standard culture techniques for retrospective diagnosis using frozen samples and for monitoring patients undergoing treatment for chronic *C. burnetii* infection [193, 194]. A diverse range of PCR assays exists for the detection of *C. burnetii* DNA in cell cultures and various clinical samples, including secretions, excretions, and tissues. These assays include light-cycler Nested PCR (LCN-PCR), conventional PCR, Real-Time PCR (qPCR), and nested PCR (nPCR) [135, 194-196].

Standard or conventional PCR represents a fundamental type of PCR reaction that yields qualitative results and necessitates a post-PCR step for the detection and visualization of DNA. A significant benefit of conventional PCR is the widespread availability of thermocyclers in research facilities, coupled with its relatively low cost. DNA sequencing denotes a method used to ascertain the sequence of nucleotide bases (Adenine, Guanine, Cytosine, and Thymine) within a DNA molecule [197]. Key applications of DNA sequencing include the analysis of protein structure and function, identification of disease-associated sequences, comparative DNA sequencing for mutation detection, and DNA fingerprinting [198].

Indirect identification of C. burnetii by serology

Since the clinical symptoms are difficult to detect especially in herd surveillance, diagnosis depends upon detection of specific antibodies can be used based on serology. Serologic methods are simpler, more rapidity and safety than isolation attempts, and are the diagnostic procedure of choice [199]. The first described of serology for detection of *C. burnetii* Phase-I and Phase-II was in 1941; however, the first applying of serology to diagnosis of Coxiella's infections among the US Army was in 1944-1945 [53, 200]. Today, several serological techniques have been described involving enzyme-linked immunosorbent assay [201], radioimmunoassay [202], immunofluorescence and complement fixation [203], indirect haemolysis test [204], microagglutination [205], in addition to dot immunoblotting and western immunoblotting [42, 206]. Criteria to be taken into account in choosing a serologic test include its specificity, sensitivity, positive predictive value, traditional availability, cost, and the amount of antigen/antibody required [207, 208]. Historically, CFT, IFAT, and ELISA are the most common applied techniques in serologic diagnosis of Coxiella's infections disease among human and animals. However, many studies demonstrated that the sensitivity of CFT was highly variable and less performing than ELISA due to several reasons such as the antigen used for CFT which utilizes only Phase-II antigen, failure to detect antibodies when anti-complementary substances are present in tested sera, and can't detect all IgG subclass [209]. The IFAT adapted for detection both phase-I and Phase-II, has better sensitivity than CFT, and relatively has a good agreement with ELISA; but also giving large proportion of dubious results and, currently, is not available commercially for animals [210].

ELISA, first used for diagnosing *C. burnetii* infections between 1983 and 1986, is among the most frequently employed diagnostic assays for detecting anti-*C. burnetii* antibodies in animals [211]. This assay is favoured in veterinary medicine due to its convenience for large-scale applications, robustness, reliability stemming from high sensitivity and specificity, availability as a ready-to-use kit, ease of execution, and commercial accessibility for detecting a mixture of anti-Phase I and II antibodies [211, 212]. The antigens (Ag) found in most commercial ELISA kits derive from two potential sources: the American Nin-mile strain or strains

sourced from the placentas of French domestic ruminants, notably sheep. The ELISA kit coated with the latter antigen exhibits greater sensitivity and is recommended for serological diagnosis, as it is commercially available for veterinary diagnostic applications to detect total antibodies, without distinguishing between anti-Phase I and anti-Phase II antibodies [213, 214].

Treatment

Although *C. burnetii* identified more than 70 years ago, it remains difficult to treat because of its absence or unspecific clinical signs in addition to the low efficacy of therapy [173, 215]. Antibiotic susceptibility testing of *C. burnetii* is also difficult as this organism is an obligate intracellular bacterium, and available data based on using three models of infection (animals, chick-embryo, and cell culture), [109]. Several studies reported that most antibiotics solely were not effective or slightly reduce the percentage of infected cells [216-218]. In addition, the long-term persistence of *C. burnetii* after acute infection with presence of different strains can result in unmanageable organism [219]. However, it has been determined that the most effective method for treating or controlling of *Coxiella* is by using more one drugs (compound) such as doxycycline with fluoroquinolone, and rifampicin with telithromycin [220-222]. Tetracycline was often used in cattle during regular procedures, either at drying off to avert late abortion or at calving to reduce vaginal shedding [216, 217, 223]. The predominant strategy involves administering two injections of oxytetracycline (20mg/kg) in the last month of gestation [224]. Nonetheless, antibiotic treatment in domestic ruminants is deemed ineffective in significantly decreasing the quantity or duration of bacterial shedding and does not completely prevent abortion and shedding of *C. burnetii* during lambing [183, 225, 226].

Control and prevention

Several direct and indirect actions are proposed to prevent spread or reduce transmission and animal/ environmental contamination. In most cases, the optimal control strategy requires a combination of several control intervention [71, 227]. The choosing of control strategy may require systemic and reliable classification to status of farm/individual to detect overall goal of the control effort [183].

Direct prophylaxis

A wide array of control methods is often used to restrict interactions during animal disease management, including quarantine, testing and culling, livestock movement regulation, and changes in farm management [228]. Owing to the characteristics of the organism, it is often challenging to affect the transmission potential within a population. During parturition or abortion, reproductive organs, fluids, and foetuses must be eradicated to avert their consumption by domestic or wild predators and the spread of illness; concurrently, aborting animals should be separated for three weeks [174]. Moreover, sheep wool might serve as a vector for infection, especially during the shearing season, due to its potential contamination with infected birthing materials [229]. Manure must be treated with lime or 0.4% calcium cyanide before to use on fields; this procedure should occur in windless conditions to prevent the dispersal of the organism [230]. Feeding places must be elevated to prevent contamination from excrement and urine [174]. Implementing trade restrictions and reducing entry of new animals from endemic regions to naïve areas or farms may mitigate danger of illness. Effective tick management is also often advised [231].

Indirect prophylaxis

In ruminants, the only method to avert the illness is the immunization of animals in infected herds, as well as those in proximity to them that are uninfected, using an effective vaccine to prevent abortions and pathogen shedding [232]. Globally, several vaccines have been developed, including formalin-killed, whole-cell vaccine preparations (WCV) and chloroform methanol-extracted bacterial residues (CMR) [233, 234]. Globally, there are vaccinations for *C. burnetii* Phase I and *C. burnetii* Phase II. Numerous studies have shown that immunization with the Phase-I vaccine may diminish placental colonization, eradicate milk shedding, and significantly decrease vaginal and fecal shedding of *C. burnetii* particles [224, 235]. Conversely, Rousset *et al*. [236] and Gharban and Yousif [237] indicated that the *C. burnetii* Phase-I vaccine is ineffective in preventing the shedding of the organism in cows who were naturally infected previous to vaccination, emphasizing vaccine's significance in safeguarding uninfected animals rather than treating those already infected. Consequently, vaccination should not be regarded as a conventional therapy, and a notable decrease in infected animals was not shown'. In a study assessing the efficacy of vaccination and/or antibiotic regimens to prevent and mitigate *C. burnetii* shedding during calving in dairy cows, Taurel *et al*. [216, 217] determined that tetracycline administration correlated with reduced shedding at calving, yet it did not significantly influence the bacterial load shed.

Conclusion

This review highlights the natural history of *C. burnetii* that appears to be endemic in several countries worldwide resulting in severe economic losses in animals and extensive health impacts in human. Therefore, furthermore investigations in the field of human and different animals are highly recommended to providing additional recent

information about the extension of *C. burnetii*, and the role of the pathogen in different infections in both domestic and wild animals and humans to creating new active schedules for control and preventing its spreading.

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Declaration of Conflict of Interest

The authors declare that there is no conflict of interest.

Ethical of approval

This study follows the ethics guidelines of the College of Veterinary Medicine, University of Wasit, Iraq (ethics approval number; CVM-WU-218/16-4-2024).

TABLE 1. Initial and recent classification of *C. burnetii*

Initial taxonomy of *C. burnetii*	**Recent taxonomy of *C. burnetii***
Domain: Bacteria	Domain: Bacteria
Subkingdom: Neqibacteria	Subkingdom: Neqibacteria
Phylum: Proteobacteria	Phylum: Proteobacteria
Class: Alpha-Proteobacteria	Class: Gamma-Proteobacteria
Order: Rickettsiales	Order: Legionellales
Family: Rickettsiaceae	Family: Coxiellaceae
Genus: *Rickettsia*	Genus: *Coxiella*
Species: *R. burnetii* [17].	Species: *C. burnetii* [19].

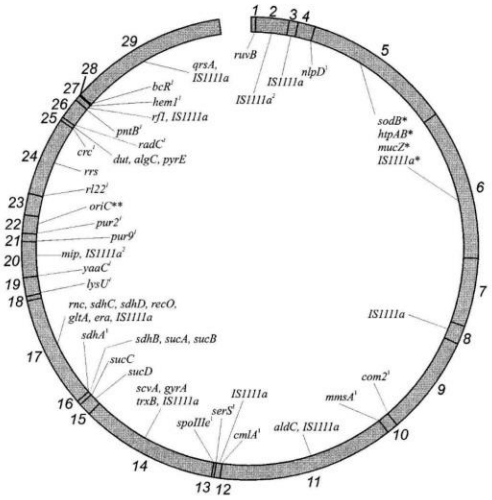

Fig. 1. Physical and genetic map of *C. burnetii* chromosome [42].

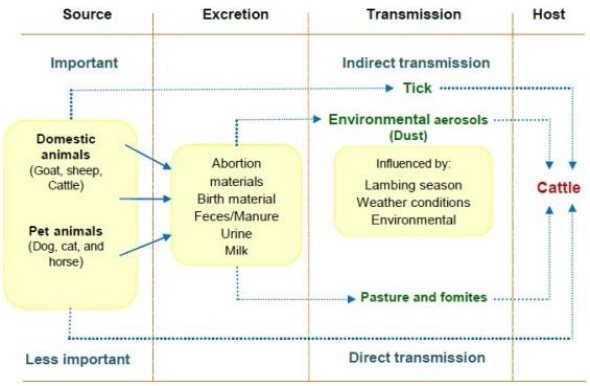

Fig. 2. Transmission model of *C. burnetii* infection to cattle.

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الكوكسيلة البورنيتية، بكتيريا معدية مهملة ذات انتشار عالمي

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الملخص

هي بكتيريا اجبارية العيش داخل الخلايا تنتشر في جميع أنحاء العالم ، مما يؤدي إلى مرض حيواني المنشأ شديد العدوى يُعرف باسم حمى كيو أو داء الكوكسيلة في نطاق واسع من العوائل بما في ذلك المجترات المنزلية والبرية والطيور والحيوانات الفأرية والمفصليات وكذلك البشر . ومن بين المجترات المنزلية ، تعد الأبقار والأغنام والماعز الخازن الرئيسي لمسبب المرض ؛ وغالبًا ما ترتبط حالات تفشي حمى كيو لدى البشر بالحيوانات الأليفة . وفي ظل ظروف الاستنبات ، تتمتع الكوكسيلة البورنيتية بمقاومة شديدة للظروف البيئية ، وتفسر هذه القدرة على تحمل الظروف القاسية قدرتها المحتملة على التسبب في مرض شديد العدوى لدى البشر واعتباره أحد عوامل الإرهاب البيولوجي . يمثل الرحم والغدد الثديية على انها الأماكن الرئيسية للعدوى ، وخاصة في المرحلة المزمنة ، ويحدث طرح الكوكسيلة البورنيتية إلى البيئة بشكل رئيسي عن طريق الإفرازات أثناء الولادة ومن خلال الحليب والبول والبراز والسائل المنوي والاستنشاق . وفي السنوات الأخيرة ، يبدو أن الكوكسيلة البورنيتية قد أستوطنت في معظم دول الشرق الأوسط . لذلك، يُوصى بشدة بإجراء دراسات في مجال الإنسان والحيوانات المختلفة لتوفير معلومات حديثة إضافية حول انتشار بكتيريا الكوكسيلة البورنيتية ، ودورها في مختلف أنواع العدوى لدى الحيوانات الأليفة والبرية والبشر ومحاولة إيجاد السبل الكفيلة بالسيطرة عليها ومنع انتشارها.

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