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Current Status of Q Fever and Its Public Health Implications: A Comprehensive Review

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Abstract Q fever is a globally significant zoonotic disease caused by *Coxiella burnetii*, an obligately intracellular, pleomorphic gram-negative bacterium. It affects various mammals, birds, arthropods, and humans, with cattle, sheep, goats, and ticks serving as primary reservoirs. The bacterium is shed in large quantities through amniotic fluid, placenta, milk, urine, and feces of infected animals, and it can persist in a spore-like form for over 40 months. Airborne transmission, environmental resilience, and high bacterial loads in infected reproductive tissues have classified *C. burnetii* as a Category B biological terrorism agent. In humans, Q fever presents in acute and chronic forms, causing endocarditis, hepatitis, pneumonia, encephalitis, meningitis, and adverse pregnancy outcomes, such as abortion and stillbirth. The disease manifests with symptoms like abortion, stillbirth, weak offspring in sheep and goats, infertility, metritis, and mastitis in cattle and camels. Diagnostic methods include bacterial isolation, serological assays, PCR, and staining techniques. Treatment involves oxytetracycline in late-gestation livestock and doxycycline as the preferred drug in humans. World Organisation for Animal Health (WOAH) has included Q fever as a notifiable disease due to its public health and economic importance. Effective control measures include vaccination, antibiotic therapy, tick control through insecticides, and rigorous hygiene practices to limit environmental contamination. In Ethiopia, where livestock is integral to livelihoods, further research is crucial to improve surveillance and implement targeted prevention strategies to mitigate its impact on public health and the economy. One Health intervention is needed to mitigate Q fever, which is an important anthropozoonosis of public health importance.

Keywords: *Biological terrorism, Coxiella burnetii, Doxycycline, Economic significance, PCR, Pubic health, Q fever*

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1. Introduction

Q fever is an anthropozoonosis of public health significance, and is reported from developing as well as developed nations of the world [1]. This zoonotic disease has been identified as a possible bioterrorism category B select agent by the Centers for Disease Control and Prevention [2]. Q fever is a globally detected disease in animals, with New Zealand being the only country reported to have an apparent zero prevalence [3]. It is particularly notable in the United States and the European Union, where the number of reported cases has increased in recent years [4]. In Africa, Q fever was first documented in 1947; however, subsequent epidemiological research on the pathogen has been limited in both quantity and quality [5]. It is important to mention that Ethiopia was ranked highest in Africa in the health burden of zoonotic diseases [6]. This reported a high seroprevalence of *Coxiella burnetii* (31.6% in cattle, 90.0% in camels, and 54.2% in goats). A 6.4% prevalence of *Coxiella burnetii* in Ethiopia was also reported from different Ixodid tick species by quantitative real-time polymerase chain reaction targeting two different genes followed by multi-spacer sequence typing (MST) [7].

Q fever is caused by *Coxiella burnetii*, the small, obligately intracellular, pleomorphic gram-negative bacterium that is characterized by high tenacity and virulence [8]. *Coxiella burnetii* can potentially survive for years in the environment, being highly resistant to chemical and physical stresses, including disinfectants,

desiccation, UV light, sonication, and osmotic stress [9]. The disease is classified as an emerging zoonotic infectious disease according to WHO, FAO, WOAH, and EFSA/ECDC [10].

Domestic ruminants, including cattle, sheep, and goats, serve as the primary reservoirs for *Coxiella burnetii* [1,11]. The principal mode of transmission of this bacterium to humans is via the inhalation of contaminated aerosols and dust particles. Less commonly, transmission may occur through direct contact with or ingestion of infected animal products, such as meat and milk. *Coxiella burnetii* is excreted in various biological fluids, including birth products (e.g., placenta), urine, milk, and feces [12]. Individuals who work in close proximity to these animals, including farmers, abattoir workers, and veterinarians, are particularly at heightened risk of exposure [1,13].

Human-to-human transmission was described and might happen through contaminated blood transfusion, sexual contact, and exposure to contaminated birth products of women [1]. Mainly, this disease is reported in humans having close contact with infected animals and their products [14]. It can manifest as an acute or chronic disease. Acute infections are mostly asymptomatic (60%) or manifest as a flu-like and often self-limiting disease. Symptoms include but are not limited to flu-like symptoms, endocarditis, hepatitis, pneumonia, abortion, [1] and premature fetal death in pregnant women and neuropathies [15], meningitis, encephalitis, and osteomyelitis [13]. Differentiation of acute from chronic Q fever based solely on clinical manifestation of the disease may be misleading. Currently, acute and chronic forms are differentiated based on different antibodies present in the sera of the patient. This demonstrates that the presence of IgG to phase I indicates the chronic form, while the detection of IgG to phase II antigen demonstrates the acute form [16]. Q fever is frequently asymptomatic in sheep and goats but causes abortion, stillbirth, premature delivery, and delivery of weak offspring, while in cattle and camels, infertility, metritis, and mastitis may develop [17].

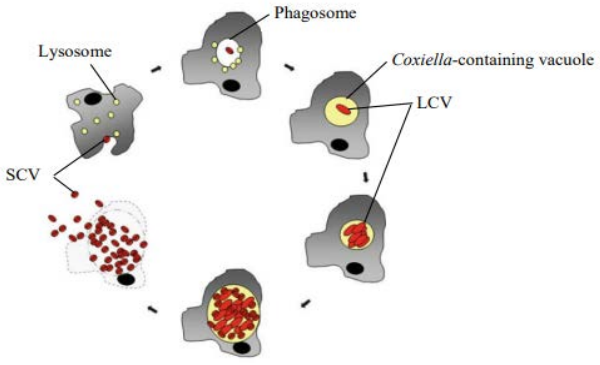
Q fever is diagnosed in the laboratory using serological tests by detection of antibodies, and polymerase chain reaction (PCR) amplification of specific targets for more accurate diagnosis [1,18]. Doxycycline is the first-line treatment for both acute and chronic Q fever in adults and children, particularly in cases of severe illness [19,20]. For pregnant patients, alternative medications such as trimethoprim and sulfamethoxazole are recommended [21]. In individuals with a tetracycline allergy or contraindication, cotrimoxazole and rifampin may be used as alternatives [22]. Although vaccination is recommended for individuals in high-risk occupations, its use is not advised for other populations due to potential side effects [23]. The economic and public health implications of Q fever remain a significant concern, particularly in developing countries, where the disease leads to substantial losses in animal productivity and presents a zoonotic risk to humans [24]. To mitigate these risks, the World Organization for Animal Health (WOAH) recommends preventive measures, including diagnostic protocols and vaccination strategies for small ruminants and cattle [25]. This communication aims to review the public health importance of Q fever, its transmission dynamics, and the preventive and control measures currently in place.

2. Literature Review

2.1. History and Morphology

The causative agent of Q fever was first described in the 1930s through two near-concurrent incidents on different continents: in Queensland, Australia, and Montana, USA [26]. Following an outbreak of undiagnosed febrile illness among abattoir workers in Brisbane, Queensland, in August 1935, Edward Derrick was tasked with investigating the cause of the epidemic [27]. In 1935, Davis and Cox, in collaboration with Derrick, confirmed the organism identified by Derrick as the causative agent of the disease, later named *Coxiella burnetii* in 1939, in recognition of the contributions of Cox and Burnet in identifying the organism as a novel rickettsial pathogen [28]. *Coxiella burnetii* was subsequently identified as the causative agent of Q Fever [29]. The disease is also referred to by several synonyms, including abattoir fever, Australian Q fever, Balkan influenza, Coxiellosis, Nine Mile fever, and pneumorickettsiosis [1,30,29].

Coxiella burnetii has two morphologically distinct cell variants an intracellular, metabolically active Large Cell Variant (LCV) and a spore-like Small Cell Variant (SCV) [31]. These two forms are morphologically and functionally distinct. The LCV is larger, elongated less electron-dense bacteria and metabolically active and replicating by a large amount [32]. While the SCV presents a compact rod-shaped with a very dense central region, and is considered metabolically dormant and less replicating [33]. SCV is resistant to environmental stress and can survive longer in harsh environments [34]. Similar to other intracellular pathogens, *Coxiella burnetii* can endure and replicate within host cells by altering the host's cellular mechanisms [35]. Despite the long generation time of up to 12 hours of replication, it follows a typical bacterial growth curve with a lag phase, exponential growth (log phase), and stationary phase [36]. Interestingly, *Coxiella burnetii* displays a biphasic developmental cycle with a replicative (LCV) and a spore-like dormant (SCV) cell form (Figure 1) [37]. During growth, these cell forms show characteristic appearance, gene expression, regulatory and structural components [38].



Source: [37]

Figure 1. Proposed biphasic developmental cycle of *Coxiella burnetii*.

2.2. Etiology and Taxonomy

Q fever is a Gram-negative, strictly intracellular, pleomorphic bacterium ranging in size from 0.2 µm to 0.5 µm in width and 0.4 µm to 1.0 µm in length. *Coxiella burnetii* is a small, obligate intracellular, pleomorphic Gram-negative bacterium that has the potential to produce infections in humans as well as animals [1]. It belongs to the domain Bacteria, phylum Proteobacteria, class Gammaproteobacteria, order Legionellales, family *Coxiellaceae*, genus *Coxiella* and species *Coxiella burnetii* [39]. *Coxiella burnetii* displays two antigenic phases based on changes that occur in the organism during in vitro culture, such as phase I and phase II [40]. Compared to other Gram-negative bacteria, Phase-I *Coxiella burnetii* antigens are more infectious and belong to the smooth phase. Whereas phase-II antigen corresponds to the less virulent granular (Rough) phase [31]. *Coxiella burnetii* was once regarded as the only species within the genus Coxiella. However, recent discoveries have led to the identification of several new species, including *Coxiella cheraxi*, found in crayfish, and a novel Coxiella-like organism present in birds and ticks. *Coxiella cheraxi* has the highest genetic homology with *Coxiella burnetii* and *Coxiella massiliensis* found in reptiles. Candidatus *Coxiella avium* is a recently identified pleomorphic Coxiella-like organism associated with avian hosts. It proliferates within the acidic vacuoles of host macrophage cells, resulting in systemic infection and increased mortality. Similarly, Coxiella-like Endosymbionts (CLE) are also present in ticks [41,42,43]. Genomic gather contains reference *Coxiella burnetii* strains separated from contaminated humans and creatures. Strain in genomic bunches 1, 2, and 3 have been disconnected from tick, human blood (intense Q fever), from the drain of diligently contaminated dairy cattle, and prematurely dead fetal tissue. Strains in genomic gather 4 and 5 have been separated from the hearts of people with incessant Q fever and tissue of prematurely dead creatures. Strains in genomic bunch 6 have been separated as they were from rodents; these strains have obscure origins and are destructive for both humans and animals [44].

2.3. Pathogenesis

Because of its high tenacity, *Coxiella burnetii* can be infectious in raw milk for 90–273 days at 4–6^{0}C as well as in raw milk products like butter and soft cheese for 42 days at 20°C. In dust and wool, its infectivity can persist for 7 to 24 months, contingent upon the ambient temperature. *Coxiella burnetii* evokes a zoonotic and mainly airborne disease called Q fever [45]. Furthermore, the organism can survive for more than 6 months in 10% salt solution [46].

The pathogenesis of *Coxiella burnetii* infection in humans and animals is not clearly understood. However, it is believed that bacterial LPS plays an important role in the pathogenesis of Q fever in both humans and animals [47]. The organism likely enters the lungs and intestines of both humans and animals through the oropharyngeal route [48]. It is highly infectious, and a very low dose is sufficient to initiate infection [49]. Following initial entry, primary multiplication occurs in the regional lymph nodes, resulting in a transitory bacteremia that lasts for five to seven days, as seen in sheep [50]. The SCVs are shed by infected animals. After infection, the organism attaches to the cell membrane of phagocytic cells. After phagocytosis, the phagosome containing the SCV fuses with the lysosome. The SCVs are metabolically activated in the acidic phagolysosome and can undergo vegetative growth to form LCVs [51]. The LCVs and the activated SCVs can be divided by binary fission and they can also undergo saprogenic differentiation. The spores produced can undergo further development to become metabolically inactive SCVs [52,53]. Both spores and SCVs can be released from the infected host cell by either cell lysis or exocytosis. The entire developmental cycle of metabolically active *Coxiella burnetii* occurs in acidic phagolysosome; therefore, *Coxiella burnetii* is resistant to microbicidal activities in the host macrophages. The acidic environment also protects *Coxiella burnetii* from the effects of antibiotics, as the efficacy of antibiotics is decreased in the acidic pH [50]. The SCV and spore forms are more difficult to denature than LCVs [54], possibly due to differences in cell wall composition and thickness as well as water content. The replicating large cell variant (LCV) of *Coxiella burnetii* and the non-replicating, infectious small cell variant (SCV) alternate during the organism's biphasic life cycle. The SCV is extremely resistant to environmental factors and has a unique spore-like shape with highly condensed chromatin [14].

2.4. Epidemiology

2.4.1. Global Distribution

Q fever is a zoonotic disease that is endemic worldwide except in New Zealand and Antarctica [55]. Its outbreaks are reported in many countries worldwide such as Egypt, Germany, the Netherlands, Switzerland and Australia [56,57]. It affects a wide range of mammals, birds, and arthropods [55] The largest Q fever outbreak ever recorded occurred in 2007 in the Netherlands, with more than 4000 acute human cases [58]. A study done in Southern Taiwan demonstrated the overall seroprevalence of Q fever as 26.3% in humans engaging in veterinary and animal-related work and exposure to goats was significantly associated with seropositivity [59, 60]. The seroprevalence studies are available from nearly all northern, western, central, eastern, and southern African countries. Nevertheless, only a few surveys were conducted with random sampling or correlated prevalence in human and animal populations [61]. Q fever seropositivity among integrated human and animal studies was 13%, 23%, 33% and 16% in Egypt [57]. Animal serological studies found that 13.9% of cattle, 12.4% of goats, and 9.4% of sheep were *Coxiella burnetii* seropositive in West Africa [62]. In Kenya, 10.5% of cattle in the outbreak were seropositive [55]. In Ethiopia, the seroprevalence of Q fever was reported as 90, 32 and 54% in camels, cattle, and goats, respectively [63].

2.4.2. Reservoirs of Q Fever

The primary reservoirs of *Coxiella burnetii* are cattle, sheep, and goats [1]. However, an increasing variety of animals have been reported to shed the bacterium,

including domestic mammals, humans, marine mammals, reptiles, ticks, and birds [64]. Despite the recognized importance of certain wildlife species, such as rabbits, red deer, and small mammals, as potential reservoirs [65], limited information is available regarding the infection in wildlife populations. In addition to these animal reservoirs, ticks play a significant role in the transmission of the pathogen and can serve as an important source of infection [66]. It has been described that one gram of tick faeces contains more than one billion Coxiella [4], and that less than ten organisms are capable of causing Q fever [23]. The bacterium has been isolated from more than 40 hard tick species, and it was demonstrated the different affinity of Mediterranean ticks for *Coxiella burnetii in Dermacentor marginatus* Sulzer, *Rhiphicephalus sanguineus* Latreille, *Rhiphicephalus pusillus* Gil Collado and *Hyalomma lusitanicum* Koch [67]. In consequence, ticks have been suggested to play an important role in the maintenance of *Coxiella burnetii* in nature, as a bridge between wild and domestic animal hosts. Vector competence for *Coxiella burnetii* has been experimentally confirmed in seven tick species: *Dermacentor andersoni* Stiles, *Haemaphysalis bispinosa* Neumann, *Haemaphysalis humerosa* Warburton and Nuttall, *Hyalomma aegyptium* L., *Hyalomma asiaticum* Schulze and Schlottke, *Ixodes holocyclus* Neumann, and *Rhipicephalus sanguineus* Latreille [23].

2.5. Risk Factors

2.5.1. Agent Factor

Coxiella burnetii can persist for a long period in the environment [1], resist physical and chemical stresses, and are easily dispersed due to a pseudo-sporulation process [51]. The severity of the infection depends on the strains of the infecting bacteria. Phase I type bacteria are more virulent than the phase II type [68]. Phase I bacteria correspond to the smooth phase (Smooth) of Gram-negative bacteria and are more highly infectious and to Phase II, to the granular phase (Rough) which has a lower virulence. Based on the Restriction Fragment Length Polymorphism (RFLP), strains of *Coxiella burnetii* are grouped into six (I-VI) genomic groups [69]. Acute infection in humans is caused by *Coxiella burnetii* genomic type I-III, whereas type IV and V are responsible for chronic infection. The virulence of type VI is unknown [21]. *Coxiella burnetii* is resistant to acids (up to PH 4.5), temperature (62°C for 30 min), UV light and pressure (up to 300,000 kPa) [46].

2.5.2. Host Factor

Prevalence is higher in dairy cows than in beef cattle. Increasing animal density increases the infection load in the environment, and this is a potential risk factor for *Coxiella burnetii* infection. Several studies in cattle show that seroprevalence increases with an increasing herd size [70]. Flock size is reported to have a similar effect in sheep [71]. A relationship of *Coxiella burnetii* infection with age and sex was also found in animals, particularly in cattle. Studies have shown that the prevalence of *Coxiella burnetii* infection increases with age or with the number of parities in cattle and sheep [72]. Age and gender are the two risk factors that are shown to influence the occurrence of Q fever in humans. People aged 30- 60 years are the most vulnerable group, and the clinical disease is mostly prevalent in men. People with a previous history of valvulopathy, an immunosuppressive disease like AIDS and pregnant women are the most susceptible [43]. People in certain occupations like veterinarians, animal farm workers, abattoir workers and laboratory personnel are at a higher risk of being infected or seropositive than others and studies show a comparatively higher prevalence in these groups [1,72].

2.5.3. Environment and Management Factors

The occurrence of human Q fever exhibits seasonal variation, although this pattern differs across geographical regions. Most cases of Q fever are reported during the spring or early summer months [73]. However, studies have suggested that the incidence of human Q fever is more closely associated with rainfall than with specific seasons [33]. A higher prevalence of Q fever has been observed among individuals living in close proximity of infected animals or in areas with high livestock density [71]. Various management factors, such as housing systems and the isolation of newly introduced animals, may also influence the seroprevalence of *Coxiella burnetii* infection in animals [70]. Q fever is considered an occupational disease among farmers, abattoir workers, and veterinarians [1], although community outbreaks have been reported around farms with infected ruminants, particularly during the kidding season [74].

2.6. Transmission and Source of Infection

The zoonotic potential of *Coxiella burnetii* originates from contact between humans and infected animals, such as wild or domestic mammals and ticks, which can shed the pathogen [1]. *Coxiella burnetii* is found in high numbers in amniotic fluid, placenta and fetal membranes as well as in milk, urine, and faeces of infected animals [1,75]. Consumption of raw/unpasteurized milk and tick bites have also been claimed as possible routes of transmission, but they are probably far less frequent than the airborne ones [76]. The main routes of introduction of *Coxiella burnetii* on a farm are the aerosolized spore-like forms transported by the wind [77]. *Coxiella burnetii* contaminated manure likely plays a role in the maintenance of infection in animal populations. Ticks may act as reservoirs of *Coxiella burnetii* in nature, as they transmit the agent transstadially and transovarially to their progeny. *Coxiella burnetii* transmission by tick bite to animals has been proposed, but this is not the most important route of infection for livestock [78]. A strong correlation has been reported between seropositivity and tick infestation in animals [79]. Maintenance of *Coxiella burnetii* infection in animal populations may be also affected by other factors such as manure management (capture, storage, treatment, and utilization), farm characteristics (herd/flock size, animal and herd/flock density) and farm environmental conditions (temperature and relative humidity) [80].

Most commonly in humans, Q fever causes a flu-like illness, which can progress to atypical pneumonia and

life-threatening acute respiratory distress syndrome [81]. Humans are at the highest risk of inhaling *Coxiella burnetii* through distant and close contact with animals, especially small ruminants [82]. The transmission of infection to human beings occurs through direct and indirect routes. Ruminants are considered the main reservoir for human infections. The direct transmission routes of infection from infected animals to humans are contact with unattended birth products and body fluids [14]. Consumption of raw milk and contact with placentae of livestock is high-risk human behavior for the acquisition of Q fever [83]. Close and distant contact between humans and small ruminants may cause single infections, as well as large outbreaks, in the human population. Animal owners, their families, and employees or veterinarians have frequented close contact with small ruminants and contaminated materials and thus are at a high risk of being infected with *Coxiella burnetii*. The most common indirect source of infection is aerosol from infected farm animals because *Coxiella burnetii* can remain in the environment over long periods [84]. As Q fever is an airborne disease, the pathogen can be spread over longer distances by wind thus posing a risk for human infection [53]. Therefore, the greatest risk of infection is within a radius of 2–4 km from the source of the pathogen. Moreover, in gale-force winds, *Coxiella burnetii* may reach distances up to 18 km [85]. Infected small ruminants can excrete the pathogen at high concentrations in abortion and birth materials, as well as at lower doses in milk, feces, urine, and semen [84]. As a result, contamination of the environment can occur, which means that *Coxiella burnetii* can be detected in dust, manure, pastures, or wool [85]. Moreover, laboratory staff may become infected via the inhalation of contaminated aerosols in workplaces [25]. As mentioned above, there are different methods of transmission of the disease. However, the primary mode of human infection involves the aerosol route, and the domesticated animals most often implicated in human disease are sheep, cattle and goats [87]. The various modes of transmission of *Coxiella burnetii* is shown in Figure 2.

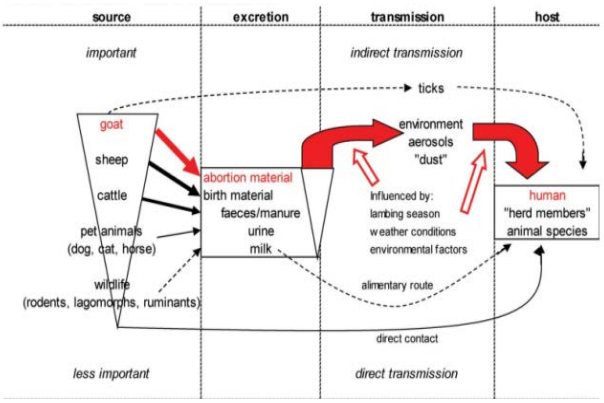


Figure 2. Transmission model for Q fever. Source: [51]

2.7. Clinical Signs

Q fever is frequently asymptomatic in animals. Sheep and goats may exhibit abortion, stillbirth, premature delivery, and delivery of weak offspring while cattle and camel may develop infertility, metritis, and mastitis. The organism is found in the blood, lungs, liver and spleen during acute experimental infection, whereas chronically infected animals persistently shed bacteria in their faeces and urine. Infection in most domestic animals remains unrecognized. Coxiellosis is considered a cause of abortion and reproductive disorders in domestic animals [88,89]. Abortion rate is comparatively higher in ewes and goats than in cows. Abortion is usually observed in late pregnancy in both ewes and cattle [90].

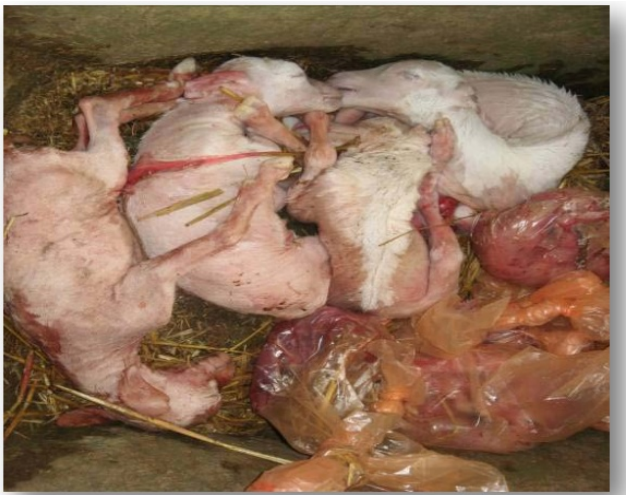


Figure 3. Abortion during late gestation due to *Coxiella burnetii* infection in a small ruminant. Sources: [91]

Coxiellosis produce both acute and chronic forms of clinical manifestations in humans. However, 60% infection remains asymptomatic with a few patients developing severe illness [92]. The acute symptoms caused by infection with *Coxiella burnetii* usually develop within 2-3 weeks of exposure [93]. Clinical signs of acute Q fever are nonspecific and vary among patients. The most common manifestation of Q fever is a self-limiting febrile illness, typically accompanied by general malaise, severe headaches, myalgia, arthralgia, chills or sweats, non-productive cough, nausea, vomiting, diarrhea, abdominal pain, and chest pain. However, it is important to emphasize that the combination, duration, and severity of these symptoms can vary significantly between individuals [94]. Children with Q fever generally have a milder acute illness than adults [64]. Although most persons with acute Q fever infection recover, others may experience serious illness with complications that include pneumonia, granulomatous hepatitis, and rarely affecting the cardiac system or central nervous system [93]. Typical pneumonia is another common symptom of acute Q fever. Pneumonia is mild in most cases is characterized by a dry cough, fever, and minimal respiratory distress. Patients may also develop hepatitis with hepatomegaly, but without jaundice, subclinical hepatitis and granulomatous hepatitis with a prolonged fever [95]. Pregnant women who are infected may be at risk for pre-term delivery, miscarriage, stillbirth or low infant birth weight. A prolonged fever, which may reach 39 to 40 ^{0}C, usually stays for 2 to 4 days and then gradually decreases to a normal level through the following 5-14 days. [95]. Chronic Q fever may develop from an acute infection. Possible predisposing factors are preexisting vascular grafts, cardiac valvulopathy, immunosuppression, and

aneurysm [96].

Manifestations of chronic disease are most commonly endocarditis (culture-negative) in patients with underlying heart valve disease, or with prosthetic valves, vascular aneurysms or vascular grafts. Chronic hepatitis is another common feature, as is chronic infection during pregnancy, chronic fatigue syndrome [97] and fever of unknown origin. Rarer manifestations are osteomyelitis, pericarditis, meningitis, Guillain–Barre syndrome, osteoarticular infections with tenosynovitis and vertebral infections [98] skin rash and chronic itch [99].

2.8. Diagnosis

The diagnosis of Q fever can only be confirmed through laboratory testing [1]. Serological tests can detect antibodies against phase I and phase II antigens of *Coxiella burnetii*, and distinguish acute from chronic disease [58]. *Coxiella burnetii* has two different antigenic Phases: Phase I and Phase II. Such an antigenic difference is important in the diagnosis. In acute cases of Q fever, the titer of antibody against Phase II is usually higher than Phase I antibody. Acute disease is mostly diagnosed via an increase in the antibody titer within three to four weeks of the onset of the disease. In comparison, in chronic cases, the titer of antibody is higher against phase I compared to phase II.

This increase in the titer of antibodies against phases I and II may persist within months to years after the first infection of this disease [64]. The clinical signs of Q fever are nonspecific both in human and animal because of this laboratory evidence of infection is needed for diagnosis. Different categories of diagnostic tests are available: Isolation of the organism, which must be conducted in a biosafety-level 3 laboratory using tissue-culture; laboratory animals, or embryonated eggs and serologic tests [30]. A variety of indirect methods (serologic assays) have been used to detect *Coxiella burnetii* antibodies in animal serum samples, including complement fixation test (CFT), enzyme linked immunosorbent assay (ELISA), micro agglutination test (MA), indirect immunofluorescence assay (IFA) and indirect fluorescent antibody test (IFAT) [51]. The complement fixation test has limited sensitivity, and the antigen employed in this test often fails to detect antibodies in sheep or goats [100]. The ELISA is more sensitive than the CFT and is able to test a higher number of animals and flocks [8]. PCR can be used to detect *Coxiella burnetii* DNA in a wide range of samples, including placental tissues, faeces, vaginal mucus and milk [100]. High level of specifity and sensitivity were acquired by PCR method with primers consisting of repetitive transposon-like element [101]. Routine diagnosis of Q fever in animals is usually established by examination of fixed impressions or smears prepared from the placenta stained by the Stamp, Gimenez or Machiavello methods, associated with serological tests [89]. *Coxiella burnetii* stains poorly with the conventional Gram stain due to its unique properties. However, Giménez staining is commonly used to effectively stain the *Coxiella burnetii* pathogen in pathological samples and tissue specimens [69]. In many countries, diagnosis of Q fever in domestic ruminants still relies mainly on modified Ziehl-Neelsen (MZN)-stained smears of placental material from aborted fetuses, supplemented by immunohistochemistry (IHC) where appropriate, although polymerase chain reaction (PCR) is increasingly being used for disease confirmation in developed countries [102].

2.9. Differential Diagnosis

There is some disease that we appreciate the same sign with Q fever such as Salmonellosis, Brucellosis, Leptospirosis, Campylobacteriosis, Listeriosis, Elective Abortion, Influenza, and Rickettsial Infection. At initial stages, i.e., before pulmonary symptoms are present, influenza may be suspected [31]. Listeriosis is called circling disease, affected animal circle in one direction only and show swallowing, fever, blindness and head pressings. There is necrosis of placenta which leads to abortion and the fetus may be macerated or delivered weak and moribund, paralysis and death follow in 2 to 3 weeks later. Listerial abortion occurs in late gestation. Brucellosis is a chronic infection that can persist for the lifetime of the affected animal. In females, it commonly leads to abortion, typically around the seventh month of gestation, and is often associated with the retention of the placenta and metritis. In males, brucellosis causes orchitis, epididymitis, synovitis, and can lead to sterility. Salmonellosis presents with clinical signs such as fever, dehydration, and foul-smelling diarrhea. In pregnant animals, it can result in abortion, especially in the last two months of gestation. Leptospirosis is characterized by clinical signs including excessive salivation, muscular rigidity, conjunctivitis, hemoglobinuria, pallor of mucous membranes, and jaundice. Leptospiral abortion occurs with or without placental degeneration and encephalitis, Abortion usually occurs 3-4 weeks later. Most affected animals are found dead, apparently from septicemia [103].

2.10. Treatment

Treatment is indicated for all infections, even for those that are subclinical. For domestic small ruminants' oral therapeutic dose may be given for 24 weeks [104]. However, most patients were treated with combination Doxycycline-hydroxychloroquine. Two injections of Oxytetracycline (20 mg per kg body weight) in the last trimester of pregnancy are usually recommended for animals, although this may not completely suppress abortions or stop bacterial shedding during parturitions. For human treatment of acute Q fever cases, a standard course of antibiotics belonging to the drug groups tetracyclines (doxycycline, glycylcycline), macrolides (erythromycin, clarithromycin, roxithromycin) and quinolones (ciprofloxacin, ofloxacin, trovafloxacin) is recommended [105]. Doxycycline is the most effective treatment for Q fever. Treatment is most effective if given within the first 3 days of symptoms, shortens the illness, and reduces the risk for severe complications [106]. If doxycycline is contraindicated due to allergies, alternative antibiotic regimens include moxifloxacin, clarithromycin, trimethoprim/sulfamethoxazole, and rifampin, each offering different spectra of activity based on the infection and patient factors.[72]. Long-term antibiotic therapy and cardiac surgery are recommended to treat chronic Q fever infection depending on the particular condition of each

patient [107]. New-generation antibiotics are being applied in clinical trials. In some pediatric cases, gamma-interferon is the treatment of choice [108]. The recommended administration for human chronic Q fever is doxycycline (100 mg per day) and hydroxychloroquine (600mg) for >18 months for adult, trimethoprim and sulfamethoxazole for >18 months for children [21]. Treatment of Q fever in pregnancy is difficult as first line antibiotics (doxycycline, hydroxychloroquine and fluoroquinolones) are contraindicated and cotrimoxazole remains the only effective antibiotic. Administration of cotrimoxazole probably prevents abortion but not the development of chronic infections or placental colonization [109]. Trimoxazole treatment of pregnant women diagnosed with acute Q fever with once daily throughout pregnancy significantly decreases the risk of adverse consequences for the fetus. In adults 100 mg of doxycycline in every 12 hours and 200mg of hydroxychloroquine in every 8 hours is indicated for chronic Q fever. Standard duration of treatment is 18 months [110].

2.11. Control and Prevention

The best methods available for control and prevention of coxiellosis are antibiotic treatment and vaccination. In the case of acute Q fever in humans, doxycycline is the antibiotic of choice [1]. For chronic Q fever, long-term treatment with doxycycline and hydrochloroquine is recommended. Although thorough evaluations of these therapies are lacking, they are considered to be effective [58]. Control options can be divided into four main groups: 1) measures to identify infected farms; 2) measures to reduce excretion of *Coxiella burnetii*; 3) measures to reduce the dispersion of *Coxiella burnetii* and 4) measures to reduce human exposure [53,56].

A prerequisite for this is the availability of adequate diagnostic tests and general practitioners and veterinarians' awareness of the presence of the disease. Notification criteria may vary per country, but notification of abortions is always one of the criteria. Measures to reduce the excretion of *Coxiella burnetii* are important for controlling human Q fever and Q fever on the farm level. Vaccination with a phase 1 vaccine is effective in reducing abortions as well as the excretion of *Coxiella burnetii* [111]. Modeling studies on the effectiveness of control measures suggest that vaccination is the most effective long-term intervention to prevent excretion of *Coxiella burnetii* on goat farms [112]. The phase I vaccine Coxevac has been effective in decreasing abortion rates and bacterial load in vaginal mucus, feces, and milk in goats [113]. Vaccination is also effective in preventing shedding of *Coxiella burnetii* in infected dairy cattle herds [114].

At human level, prevention of exposure to animals or wearing gloves, boots, and masks during manipulation of animals. Pasteurization at 145°F (63° C) for at least 30 minutes or 161°F (72°C) for 15 seconds of sterilization is sufficient to destroy *Coxiella burnetii*, as well as other pathogens that can be present in raw milk [115]. Vaccination may also be considered in livestock handlers, processors of animal products, veterinarians and laboratory workers likely to handle infected specimens [116]. *Coxiella burnetii* is able to survive for long periods in the environment and in wild animals. The only way to prevent the disease in ruminants is to vaccinate uninfected flocks, with an efficient vaccine. Three types of vaccine have been proposed for providing human protection against Q fever: the attenuated live vaccine (produced and trialed in Russia but subsequently abandoned because of concern about its safety); chloroform methanol residue extracted vaccine or other extracted vaccines (trialed in animals but not humans); and the whole cell formalin inactivated vaccine, which is considered acceptably safe for humans [117].

Coxiella burnetii can be reduced in the farm environment by regular cleaning and disinfection of animal facilities, with particular care of parturition areas, using 10% sodium hypochlorite. In the UK, Health Protection Agency guidelines mention the use of 2% Formaldehyde, 1% Lysol, 5% Hydrogen peroxide, 70% Ethanol, or 5% Chloroform for decontamination of surfaces. Appropriate tick control strategies and good hygiene practice can decrease environmental contamination. Infected fetal fluids and membranes, aborted fetuses and contaminated bedding should be incinerated or buried. Additionally, manure should be treated with lime or a 0.4% calcium cyanide solution before field application, ensuring the treatment occurs in windless conditions to prevent the dispersion of microorganisms over a wide area. In feed addition of tetracycline or injectable oxytetracycline prepartum has not been shown to prevent *Coxiella burnetii* shedding in feces, milk, and vaginal secretions [117]. Preventive vaccination, manure management including covering and compositing of manure or treating manure with lime, better livestock farm and wool shearing practices, use of isolated calving pens, restrictions on free animal movement and proper disposal and burial of aborted materials are important measures to prevent the spread of *Coxiella burnetii* infection. Hygienic practices, especially calving pen cleanliness, is considered an important measure in preventing this infection. Similarly, disinfection of calving pens, naval cord disinfection, and proper disposal of aborted fetuses and fetal membranes, and provision of new bedding at the time of calving are important measures to reduce the risk of disease transmission. Birth products including fetal membranes and dead fetuses should immediately be disposed to avoid their ingestion by stray dogs, wild carnivores and even domesticated animals, which may also spread the infection in the environment [118,119,120]. The health education of various occupational groups, such as abattoir workers, dairy farmers, shepherds, wool sorters, tanners and veterinary professions about the source of infection, mode of transmission, severity of disease and personal hygiene should be imparted [1].

3. Status of Q fever in Ethiopia

According to a few studies conducted in Ethiopia, 6.5% of abattoir workers in Addis Ababa had *Coxiella burnetii* on their bodies. Additionally, sheep and goats slaughtered at the Addis Abeba abattoir and its peri-urban areas were found to have antibodies against *Coxiella burnetii [7]*. A seroprevalence of 31.6, 90, and 54.2% of *Coxiella burnetii*

was recorded in cattle, camels and goats respectively in South Eastern Ethiopian pastoral zones of the Somali and Oromia regional states. Ticks were tested for *Coxiella burnetii* in Ethiopia by quantitative real time polymerase chain reaction targeting two different genes followed by multispacer sequence typing (MST). An overall prevalence of 6.4% of *Coxiella burnetii* was recorded. *Coxiella burnetii* was detected in 28.6% of *Amblyomma gemma*, 25% of *Rhipicephalus pulchellus*, 7.1% of *Hyalomma marginatum rufipes*, 3.2% of *Amblyomma variegatum*, 3.1% of *Amblyomma cohaerens*, 1.6% of *Rhihipicephalus praetextatus*, and 0.6% of *Rhipicephalus (Boophilus*) decoloratus. Significantly higher overall frequencies of *Coxiella burnetii* DNA were observed in *Amblyomma gemma* and *Rhihipicephalus pulchellus* than in other tick species [121]. It also seroprevalence of 6.17 and 11.79 *Coxiella burnetii* was reported in dairy farms and slaughterhouses, respectively in Jimma town, South Western Ethiopia [122]. Abortion is one of the most important reproductive health problems of dairy cows in Ethiopia in terms of economic impact. Both infectious and non-infectious agents may cause abortion in cattle. Q fever is one of infectious diseases, which causes abortion in Ethiopia [123].

4. Public Health Importance

Human population is at high risk of acquiring emerging infectious diseases particularly those of zoonotic nature [1,124]. Among zoonotic diseases, Q fever is of great significance with special reference to human public health. The causative agent of Q fever is *Coxiella burnetii* , which is a Gram-negative bacterium. It is a highly infectious disease that poses a significant risk to certain occupational groups, including veterinarians, laboratory personnel, farmers, and abattoir workers [1]. Studies have revealed that a considerable proportion of livestock handlers possess antibodies indicative of prior exposure to the causative organism. While less than half of those exposed develop symptoms, the disease typically manifests as mild. However, in symptomatic cases, individuals may experience high fever, headache, muscle pain, sore throat, nausea, vomiting, and abdominal or chest pain. The fever can persist for one to two weeks and may progress to complications such as pneumonia or liver involvement. Individuals with compromised immune systems or pre-existing heart valve conditions are particularly susceptible to severe outcomes, which can be fatal. Additionally, a chronic post-Q fever fatigue syndrome may develop in some cases. Q fever is the second most commonly reported laboratory infection with several recorded outbreaks involving 15 or more persons. Human infection occurs due to inhalation of dust contaminated by infected animal fluids, consumption of unpasteurized dairy products and contact with milk, urine, faeces, vaginal mucus or semen of infected animals [1,79]. In humans, initial exposure to *Coxiella burnetii* may result in asymptomatic or mild infection but also in acute or chronic disease [43]. The clinical diagnosis can be challenging. The reasons for this high clinical polymorphism are largely unknown, even if risk factors of severity (Example: pregnancy, immunosuppression, preexisting cardiac valvulopathy, vascular grafts, and aneurysms) have been described. Although rarely fatal, the disease may lead to substantial morbidity and can be highly debilitating, even under treatment [89].

5. Conclusion and Recommendations

Q fever is a globally significant health concern and a notifiable disease under the World Organisation for Animal Health (WOAH). It is recognized as an infectious disease of considerable economic and public health importance. Notably, Q fever ranks as the second most commonly reported laboratory-acquired infection. Farm animals, including cattle, goats, and sheep, are the primary sources of human infection, although wild animals and pets have also been implicated in outbreaks. The disease is primarily transmitted through contaminated dust containing feces, urine, milk, or ticks. *Coxiella burnetii*, the causative agent, exhibits exceptional resistance to environmental conditions and disinfectants, enabling it to survive for extended periods. Transmission occurs through direct contact with animal reproductive materials or via aerosols, posing a risk to both humans and animals. Vaccination against Q fever and treatment with tetracycline antibiotics are recommended measures for disease management. Additional control strategies include the use of insecticides to manage tick populations and adherence to strict hygiene practices to minimize the risk of disease transmission. Therefore, based on the above conclusion the following recommendations are suggested:-

- Public education about potential sources of infection and the promotion of consuming only pasteurized milk and dairy products.
- It is advised to immunize people who are occupationally exposed, including veterinary professionals, livestock handlers, and abattoir workers.
- Vaccination of animals identified in endemic areas should be prioritized by the government.
- Public awareness campaigns should emphasize the importance of using insecticides as an effective measure to control tick populations.

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