Epidemiology and public health implications of Q fever

Angesom Hadush[1], Venkataramana Kandi[2], Mahendra Pal[3]

[1]Assistant Professor, Samara University, College of Veterinary Medicine, P.O. Box 132, Samara, Ethiopia, [2] Assistant Professor, Department of Microbiology, Prathima Institute of Medical Sciences, Karimnagar, Telangana, India, [3]Ex- Professor, Addis Ababa University, College of Veterinary Medicine, P.O.Box.34, Debre Zeit, Ethiopia.

Corresponding author: Prof. Mahendra Pal, Ex-Professor of Veterinary Public Health (UNDP), Addis Ababa University, College of Veterinary Medicine, P.O.Box.34, Debre Zeit, Ethiopia.

Email ID: palmahendra2@gmail.com

ABSTRACT

Zoonotic diseases remain a significant cause of morbidity and mortality throughout the world. Q fever is considered as an emerging and re-emerging zoonosis of global concern. Disease is caused by *Coxiella burnetii,* an intracellular, Gram negative organism, which is prevalent throughout the world. Despite the fact that Q fever is important from public health and economic point of view, it remains poorly reported and its surveillance is mostly neglected. It has extensive reservoirs that include mammals, birds, and arthropods, mainly the ticks. Domestic ruminants are considered as the main reservoirs for the pathogen, which can infect wide range of hosts. *Coxiella burnetii* can cause reproductive problems in domestic animals. During an abortion in animal, about 1 billion *C. burnetii* per gram of placenta are excreted. Different mode of transmission is observed in Q fever. Disease outbreaks have been associated with slaughterhouses, farms, and institutions with intensive sheep rearing programs. The clinical manifestations of Q fever range from no symptoms to pneumonia, hepatitis, and endocarditis. Because the clinical signs of Q fever are nonspecific, laboratory evidence of infection is needed for making an unequivocal diagnosis. A number of antibiotics such as doxycycline, erythromycin, and clarithromycin are helpful in the treatment of patient. Fatality rate in untreated patients is high. Since human-to-human transmission is extremely rare and Q fever is mainly an airborne disease, measures of prevention are aimed at avoiding the exposure of humans and particularly persons at risk, to animal and environmental contamination. Therefore, improvements in surveillance, such as increasing medical reporting, and making animal infections notifiable is needed. It is emphasized to undertake detailed comprehensive study to determine the prevalence and incidence of Q fever, which has emerged as a significant public health problem in many regions of the world.

Keywords: *Coxiella burnetii,* Human, Q fever, Reservoirs, Zoonosis.

INTRODUCTION

Zoonoses are defined as those diseases and infections, which are naturally transmitted between man and vertebrate animals. Presently, over 300 zoonotic diseases of multiple etiologies are described from developing and developed nations of the world[1]. A plethora of factors are responsible for the emergence and re-emergence of zoonoses. These diseases result in high morbidity and mortality both in humans and a wide variety of animals and hence are receiving global attention of public health authorities[2]. Among these, Q fever is a zoonotic disease first identified in Queensland, Australia, in 1935, after an outbreak of febrile illness among slaughterhouse workers[1]. The disease was named "Query" fever, because its etiopathogenesis was not known. It is also known by several synonyms such as abattoir fever, Australian Q fever, Balkan influenza, Coxiellosis, Nine-mile fever, and Pneumoricke ttsiosis[1].

Q fever is a global public health concern, as is reported from more than 59 countries of the world[3]. While Q fever is an OIE notifiable disease, it remains poorly reported, and its surveillance is frequently severely neglected. Domestic ruminants such as cattle, sheep, and goats are considered as the main reservoir for the pathogen[4], which can infect a large variety of hosts including mammals (humans, ruminants, small rodents, dogs, and cats), avians, fishes, reptiles, and arthropods. It was reported to be a highly infectious disease in guinea pigs during experimental intraperitoneal infections. Both in animals and humans, however, Q fever infections remain poorly understood, and their prevalence has been underestimated for many years[5].

In 1935, researchers in the United States isolated a rickettsial agent from ticks that they called Nine Mile agent, which was subsequently linked to a laboratory-acquired human infection. The agents were later determined to be identical, and were eventually named *Coxiella burnetii* in honor of Harold Cox and MacFarlane Burnet, two prominent early researchers. *Coxiella burnetii* is most commonly transmitted to humans by direct contact with the reproductive tissues of cattle, sheep, and goats in which the causative organism reaches

exceptionally high titers. Disease outbreaks have been associated with slaughterhouses, farms, and institutions with intensive sheep research programmes. Sporadic human infections have also been linked to parturient domestic animals, such as dogs and cats. Aerosol transmission of *C. burnetii* occurs through the inhalation of contaminated materials and large human outbreaks have been linked to wind dispersion from sites where infected animals are kept[6]. Hence, the objective of this communication is to review Q fever as emerging and re emerging rickettsial zoonosis of global significance.

Etiology

Q fever is caused by obligate intracellular bacteria called *Coxiella burnetii*[7]. The agent differs from other rickettsiae in its filterability and high degree of resistance to physical and chemical agents. It has been found to have several different plasmids, the functions of which are not yet understood. *Coxilla burnetii* can be highly pleomorphic when it reproduces inside the phagolysosomes of an invaded host cell. Two different forms can be distinguished under an electron microscope: one, large and bacilliform, and the other, coccoid, which develops from the former and has greater electronic density. A third form appears in the large cells after passage through embryonated eggs or BGM cell cultures when they have been kept in suboptimal temperature conditions or fresh medium has not been added. These small, high-density forms are similar to spores. The morphogenesis is comparable, but not identical, to cell differentiation in the formation of endospores. These small forms are responsible for the high resistance of the agent to environmental factors and many disinfectants[8].

Routes of infection and mode of transmission

Inhalation is the most common route of infection in both humans and animals. Under experimental conditions, inhalation of a single *C. burnetii* can produce infection and clinical disease in humans. However, similar studies have not been done in animals. As mentioned above, domestic animals are considered the main reservoir for the pathogen that can contaminate the environment by shedding *C. burnetii in milk,* feces, urine, saliva, and very importantly in vaginal secretions, placenta, amniotic fluids, and other products of conception. *Coxiella burnetii* also spreads by wind causing infections at a distance from the initial source of bacteria. In domestic ruminants, milk is the most frequent route of pathogen shedding. Currently, controversy remains concerning the possibility of infection by oral route. Results of previous studies on the subject are considered inconclusive. OIE advises not to drink raw milk originating from the infected livestock farms[9].

Human-to-human transmission does not usually occur although it has been described following contact with parturient women. In addition, cases of sexual transmission of Q fever have been reported. Currently, risk of transmission through blood transfusion is considered negligible. Transplacental transmission, intradermal inoculation, and postmortem examinations have been associated with sporadic cases of Q fever. The natural infection has also been observed in more than 40 species of ticks from the families Ixodidae and Argasidae, as well as other arthropods that feed on animals. However, even if infected, not all tick species are able to serve as vectors and transmit the infection to vertebrates. The relationship between the two cycles of infection is not well studied. There are indications that domestic animals may contract the infection through infected ticks coming from natural foci, but the infection in domestic animals is not dependent on this mechanism; it can be perpetuated independently. The most common mode by which the infection is transmitted between domestic animals is through the inhalation of aerosols from contaminated placental material, amniotic fluid, and excreta [9, 10].

Clinical signs in humans

The incubation period ranges from two weeks to 39 days, with an average of 20 days. The disease has a sudden onset, with fever, chills, profuse sweating, malaise, anorexia, myalgia, and sometimes nausea and vomiting[1]. The fever is remittent and usually lasts from 9 to 14 days. A prominent symptom of the disease is severe cephalalgia, and retro orbital pain is common. In about half the patients, X-ray examination reveals pneumonitis, which manifests itself clinically in the form of a slight cough, mild expectoration and occasionally, chest pain. About 50% of patients have gastrointestinal problems, such as nausea, vomiting, or diarrhea. Acute hepatitis can also occur. In contrast to the other rickettsioses, Q fever does not cause a cutaneous rash. The disease ranges in severity, but in most cases it is benign. Many human infections are mild and inapparent and thus go undetected. Q fever rarely attacks children under 10 years old. However, in the Netherlands, 18 cases in children under 3 years old were reported within a 16-month period [11].

The disease is more serious in adults over 40 years of age. The case fatality rate for acute Q fever is less than 1%. A retrospective study of Q fever patients in France (1,070 acute cases during 1985–1998) found that different clinical forms of acute Q fever were associated with different patient statuses. Isolated fever occurred more frequently in females, hepatitis occurred among younger patients, and pneumonia occurred in older or immunocompromised patients. When the disease takes a chronic course, it mainly affects the cardiovascular system[12].

Disease in animals

As a general rule, the infection in domestic animals is clinically inapparent. In ruminants, after *C. burnetii* has invaded the bloodstream, it becomes localized in the mammary glands, the supramammary lymph nodes, and the placenta. Many cows get rid of the infection after a few months, but others become

carriers, with the agent localized in the mammary glands and eliminated throughout many lactation periods. During calving, a large number of rickettsiae are shed with the placenta, and, to a lesser degree, the amniotic fluid, feces, and urine. The agent's strong resistance to environmental factors ensures its survival, as well as the infection of new susceptible animals and man. Activation of the infection during calving, with massive shedding of the agent in various secretions and excretions, explains why many sporadic outbreaks in man coincide with that period. Usually, neither milk production nor development of the fetus or the newborn animal is affected by the infection[12]. Main clinical manifestations of disease in goats and sheep are abortion and still birth, where as in cattle, it is associated with abortion, metritis, and sub-fertility[1, 13].

Diagnosis

Because the clinical signs of Q fever are nonspecific, laboratory evidence of infection is needed for diagnosis. Four categories of diagnostic tests are available: isolation of the organism, which must be conducted in a biosafety-level laboratory using tissue-culture; laboratory animals, or embryonated eggs; serologic tests, including indirect fluorescent antibody (IFA), enzyme immunoassay, and complement fixation; antigen detection assays, including immunohistochemical staining (IHC), and nucleic acid detection assays, including polymerase chain reaction (PCR) assays[1]. In humans, acute Q fever is most commonly diagnosed by use of IFA. Because antibodies against Q fever may develop late in the clinical course of disease, paired serum specimens should be tested; evidence of IgG antibody seroconversion or the presence of IgM antibody indicates recent acute infection. During acute infection, the body produces higher antibody concentrations to *C. burnetii* phase II antigen. Titers are highest to phase I antigen in chronic infections, and the IgG phase II: I antibody ratio is widely used to distinguish acute from chronic infection. Culture, IHC, and PCR can be used to detect *C .burnetii* in heart valve tissue from patients with endocarditis. Culture, and PCR have also been used to diagnose acute or chronic Q fever by using whole blood samples; however, the diagnostic sensitivity of these techniques is lowered by prior antimicrobial administration[14].

Epidemiology

Q fever is a worldwide zoonosis, which may occur in sporadic as well as epidemic forms. It may be emerging disease, probably related to climate change. Very recently, Dave and others published a review on the impact of climate change on the emergence of human vector borne diseases[14]. Many animals and arthropods act as reservoirs of infection. However, the most commonly identified sources of human infections are farm animals such as cattle, goats, and sheep. Pets, including cats, rabbits, and dogs, have also been demonstrated to be potential sources of urban outbreaks of disease [4, 13, 16]. Cats are suspected as an important reservoir of *C. burnetii* in urban areas and may be the source of urban outbreaks. In Canada, 6 to 20% of cats have anti *C. burnetii* antibodies. Wild rat has been suspected as an important reservoir of *C. burnetii* in Great Britain [17, 18].

All these mammals, when infected, shed the desiccation-resistant organisms in urine, feces, milk, and, especially, birth products. Reactivation of infection occurs in female mammals during pregnancy. Q fever causes abortions in goats and, less frequently, sheep and causes reproductive problems in cattle. High concentrations of *C. burnetii* are found in the placentas of infected animals. Due to its resistance to physical agents, *C. burnetii* can survive for long periods in the environment[19].

In Europe, acute Q fever cases are more frequently reported in spring and early summer. They may occur at all ages, but they are more frequent in men than in women. Q fever is usually benign, but mortality occurs in 1 to 11% of patients with chronic Q fever. *C. burnetii* is endemic in every part of the world except New Zealand. Since the clinical presentation is very pleomorphic and nonspecific, the incidence of Q fever among humans is probably underestimated, and diagnosis particularly relies upon the physician's awareness of the symptoms of Q fever and the presence of a reliable diagnostic laboratory. In southern France, 5 to 8% of cases of endocarditis are due to *C. burnetii*, and the prevalence of acute Q fever is 50 cases per 100,000 inhabitants. The disease is also reported in many African and Asian countries[17]. Q fever is an important occupational zoonosis of abattoir workers, butchers, shepherd, livestock handlers, and veterinarians [2, 7, 19].

Treatment

In nonpregnant women and other patients with acute Q fever, treatment consists in a daily dose of 200?mg doxycycline for 14 to 21 days. Hydroxychloroquine can be associated with doxycycline. Hydroxychloroquine increases the pH of the phagolysosomes, and its association with doxycycline has a bactericidal effect. Rifampin, erythromycin, clarithromycin, and roxithromycin can also be used as an alternative treatment[1]. Fluoroquinolones are recommended in cases of meningoencephalitis as their penetration into the central nervous system is better compared to doxycycline. Treatment with IFN? has proven effective in certain population groups [20].

Prevention and control

Since human-to-human transmission is extremely rare, and Q fever is mainly an airborne disease, measures of prevention are aimed at avoiding the exposure of humans and particularly persons at risk, to animal and environmental contamination. To prevent and reduce the animal and

environmental contamination, several actions can be proposed. Specific caution must be taken when introducing a new animal into a Q fever free flock, in order to avoid the spread of infection. An antibody investigation for Q fever should be performed in the flock of the seller and animals from seropositive flocks can only be introduced in seropositive or vaccinated flocks. Since parturition is critical for the transmission of the disease, in infected flocks, birth must take place in a specific location, which must be disinfected as well as every utensil used for delivery. Placentas and fetuses must be picked up and destroyed as soon as possible in order to prevent their ingestion by domestic or wild carnivores, which could disseminate the pathogen by wearing protective gears, i.e. gloves, boots, masks[1]. Manure must be covered and composted or treated with lime or calcium cyanamide 0.4% before being spread on the field[1]. Several vaccines have been developed to protect high-risk occupational groups such as workers in laboratories, abattoirs, wool-shearing sheds, and on farms, as well as patients with heart valve implants and immunodeficient individuals[21].

Recent advances in Q fever research

A recent paper reported the complete genomic picture of *C. burnetii* isolated from a human outbreak involving more than 4000 cases. This study has observed that the strains isolated from human cases were epidemiologically linked to the goat outbreak strain. This report re-emphasizes the importance of Q fever and its importance as a frequent zoonotic disease[22]. *Coxiella burnetii,* and its ability to cause infection by altering immune mechanism was established in a recent in-vitro study. This study has infected the monocytes derived macrophages with virulent strains of *C. burnetii* and found that *C. burnetii* could down regulate the release of pro-inflammatory markers such as interleukin-1ß (IL-1ß), IL-12, and tumor necrosis factor alpha (TNF-a) and inhibited the expression of T cell activation markers including the CD40, CD80, CD86 and the major histocompatibility complex (MHC) [23]. Post outbreak air sampling study from the Netherlands has showed the presence *C. burnetii* after 1 year of outbreak and its presence was high during goat kidding periods. This study highlights the importance of animal rearing environments and its potential role in transmission of Q fever to humans[24]. It was also recently established that C. burnetii can be present in two morphological forms including the large cell variant (LCV) and the small cell variant (SCV). It was noted that C. burnetii survives in the environment as SCV's due to the presence condensed nucleoid and an unusual cell covering[25]. Previous research has noted that only *C. burnetii* can survive in the acidic, high proteolytic, and oxidative environments of the phagolysosomes and thereby evades innate immune responses. It was also noted that *C. burnetii* could secrete toxic elements which help them to fight the adaptive immune mechanisms of humans and animals[26, 27]. With the advances in the molecular methods and also an improvement in the culture techniques (growing *C. burnetii* in cell free medium), research on *C burnetii* has increased and there is now improved understanding of the modes of transmission and pathogenesis of Q fever [28, 29]. A study performed in insect model Galleria mellonella, has revealed that *C. burnetii* multiplies inside the host cells by forming a large Coxiella-containing vacuole (CCV) and secretes a protein named Coxiella vacuolar protein B (CvpB). CvpB helps in binding and expanding of the vacuole and modulates phosphoinositide metabolism so as to survive and develop inside the cell[30].

CONCLUSION

Q fever is a zoonotic illness having a global public health importance. Domestic ruminants are considered the main reservoir for *C. burnetii.* The causative agent is transmitted to humans through direct contact with reproductive products of animals. Aerosol transmission of the disease occurs through the inhalation of contaminated materials, and large human outbreaks have been linked to wind dispersion from sites where infected animals are kept. In the absence of the specific clinical signs, laboratory help is imperative to confirm an unequivocal diagnosis of disease. Therefore, the risk for transmission can be decreased through attention to proper sanitation when dealing with parturient animals and ensuring proper pasteurization of milk products. Immunization of occupationally exposed persons, such as abattoir workers, livestock handlers, veterinarians etc. is advised. It is highly imperative that clinically suspected animals in the farm should be prudently investigated for tracing the source of human infection. Serological investigation of wildlife should be conducted to identify the reservoirs of Q fever infection. Moreover, systematic studies are mandatory to know the current status of the disease worldwide.

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