*Asian Journal of Research in Animal and Veterinary Sciences*

*8(2): 8-14, 2021; Article no.AJRAVS.68215*

# Overview: Q Fever and Potential Emerging Infection in Ruminants and Risk of Zoonotic Transmission

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***Authors' contributions***

*The sole author designed, analyzed, interpreted and prepared the manuscript.*

***Article Information***

Editor(s):
(1) Prof. Hazem Mohammed Ebraheem Shaheen, Damanhour University, Egypt.
(2) Dr. Fabio da Costa Henry, State University of Northern of Rio de Janeiro, Brazil.
Reviewers:
(1) Mohamed M Rhagem, University of Zawia, Libya.
(2) Shakeeb Ullah, Gomal University, Pakistan.
Complete Peer review History: http://www.sdiarticle4.com/review-history/68215

***Mini-review Article***

***Received 20 March 2021***
***Accepted 25 May 2021***
***Published 27 May 2021***

## ABSTRACT

Q fever is an economically significant disease in ruminants causing a range of reproductive disorders worldwide. The disease has not been reported in ruminants while low seroprevalence was reported among humans in Sri Lanka. Since factors associated with antibody against *Coxiella burnetti* in human has not been found and the association between human and animal has not been evaluated. However, importation of live animals may or may not be considered as a potential risk factor therefore, extensive studies are encouraged.

Q fever is caused by obligate intracellular parasite *Coxiella burnetti* which is an aerobic, Gram-negative organism, and highly resistant bacterium. The bacterium may infect mammals, birds, and arthropods. Q fever has been reported slightly high prevalence in cattle than in small ruminants, the disease is often considered a a neglected disease in differential diagnosis in the clinics and laboratories. Q fever is mainly associated with reproductive disorders such as abortion, metritis, weak offspring, and sterility. The organism also causes mastitis in cows. The risk of transmission is highly dependent upon the prevalence of shedders in a herd and intensity of shedding the organism by animals. Although herd size and composition of herd has been identified as no effect on epidemiology, herd density is considered an important factor in transmission of the disease within the herd. *Coxiella burnetti* is shed through birth products, vaginal fluids, urine, feces, and milk just after calving or parturition. The Q fever has been reported in most of the countries in the World. High

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seroprevalence was reported in Belgium where prevalence was 56.7%. The prevalence of Q fever at individual and herd level in France was 20% to 38% in cattle and 15% and 25% in sheep and goats respectively. In the USA, herd prevalence of Q fever was varied from 26.3% to 94.3% in 2002 and 16.7 and 5.4% in 2011, Asia. Cats are considered as the main source of human infection comparing to dogs. The bacterium had been isolated from feline vaginal mucosa and associated with reproductive disorders including abortion in cats. Inhalation has been identified as the main source of transmission both in animals and humans, infective material is infected through inhalation. Ingestion and vertical transmission have been also suspected. The organism is considered to be highly resistant in a farming environment for 2 years of post-infection.

The infection is often asymptomatic in humans and both acute and chronic forms have been reported flu-like infection, pneumonia, and hepatitis were reported common and chronic fatigues, endocarditis, pneumonia, abortion, stillbirth, and premature deliveries, were also reported. Most clinical cases reported were among the immunocompromised population, abattoir workers, farmworkers, and people who have a close association with animals. Also, a good prognosis has been observed in humans when treatment was started at early stage. High seroprevalence was reported among veterinarians and vaccination with Phase I vaccine was proven results on developing clinical disease, although side effects were reported on people who exposed to the organism previously. Fluoroquinolone was recommended only for meningoencephalitis and other human cases were treated with doxycycline, trimethoprim-sulfamethoxazole, and hydroxychloroquine.

Both humoral and cell-mediated immune mechanisms were recognized as an essential tool to protect against *Coxiella burnetti* infection in animals and humans. Passive actin-dependent phagocytosis in phagocyte cells and active zipper mechanism in nonphagocytic cells have been described in pathogenesis. The bacterium can be detected in different clinical samples such as milk, vaginal mucous, feces, urine, semen, birth fluid, and placental membranes. Identification of the bacterium can be done by conventional bacteriological methods; molecular methods and detection of antibodies were done by serological methods such as ELISA. Identification of the organism and serological diagnosis in bulk milk tanks is the most practical way of diagnosis in ruminants. Serological diagnosis is considered the gold standard of diagnosis of Q fever in humans. Antibiotics, vaccination, and a combination of these two are the alternative to control clinical disease in cattle. A few vaccine types have been recognized such as inactivated PI or PII, attenuated PII *Coxiella burnetii.* Chloroform: methanol residue fraction of Nine Mile phase I killed vaccine and used to control the excretion of the organism in sheep/goat and cattle.

*Keywords: Zoonotic transmission; reproductive disorders; cattle; animal disease.*

## 1. INTRODUCTION

Importing dairy cattle has been done as a priority practiced in recent dairy industry to improve genetic potential and to increase number of milking cows in the country. A couple of thousand cows were imported from Australia and New Zealand to government farms, large-scale farms, and medium-scale private farms around the country. In addition, private entrepreneurs would like to import from India, Denmark, and Australia in future, although government policy has not been declared yet. Furthermore, around 100 goats were imported from Australia. Although no -post-import evaluation has been performed, animal health authority faces huge challenges when importing animals in large numbers such as screening of new or introducing diseases due to lack of laboratory infrastructure, shortage of diagnostic equipment, chemical and media, limited trained human resources. Importantly, testing for several diseases within a short period is a challenging task without having proper optimization, positive & negative control on time. Although no extensive investigations were carried out and no technical report has been published on introduced animal diseases because of the importation of live animals. However, author assumes that Q fever is a potential disease in which ruminants may come across a risk in future.

Q fever has not been reported among ruminants in Sri Lanka which has potential risk as an emerging disease in dairy industry. There is no screening mechanism or surveillance program to identify Q fever in ruminants at present. However, Q fever has been reported in humans and 1.6% of patients with skin rashes were shown antibodies against *Coxiella burnetti* in Sri

Lanka [1]. Furthermore, no reports are found about ruminants in the country either with clinical or subclinical infections. According to the Invasive Species Compendium, which is a source of useful information, *Coxiella burnetti* has not been reported in the country (cabi.org).

## 2. MICROBIOLOGY OF *COXIELLE BURNETTI*

Q fever was first described in 1937 and recognized as highly infectious disease worldwide [2]. Q fever is caused by obligate intracellular parasite *Coxiella burnetti* in cattle [3]. *Coxiella burnetti* is an aerobic, Gram-negative organism, and highly resistant bacterium that may infect mammals, birds, and arthropods [4]. In the literature, the organism as pleomorphic coccobacillus in size of 0.2–0.4 mm wide, 0.4–1 mm long [5]. Two dominant phase variations have been identified in *Coxiella burneitti* as Phase I infectious form and Phase II non-infectious form when sub cultured in medium such as cells and embryonated eggs [6]. Importantly, ticks are considered as main reservoirs of this organism [6]. *Coxiella burnetti* is the only known intracellular bacterium that replicates within eucaryotic phagolysosome [5]. Furthermore*, Coxiella burnetti* is phylogenetically related to *Legionellae* species and *Francisella tularensis* two pathogenic organisms in animals [6].

### 2.1 Epidemiology

Q fever is considered as slightly high prevalence in cattle than in small ruminants and it often is considered as neglected in differential diagnosis in ruminants [7]. The organism was also reported in pets such as dogs and cats [8]. In addition, *Coxiella burnetti* has also been isolated from rodents, reptiles, and fish [2].

This is an endemic disease worldwide except in New Zealand, although the disease in animals has not been reported in Sri Lanka yet [3]. The uterus and mammary gland were the predominant site of localization of this organism [9]. Q fever is mainly associated with reproductive disorders such as abortion, metritis, weak offspring, and sterility. In addition, it causes mastitis in cows [10]. It has been also noticed that *Coxiella burnetti* was caused sporadic abortion in cows [10]. Furthermore, placental necrosis, fetal bronchopneumonia were common in calves [10]. In a herd, risk of transmission is highly dependent upon prevalence of shedder in a herd and intensity of shedding the organism in cattle [3,11]. In addition, a ratio of susceptibility against immunity seems to have a vital role in host pathogen interaction in Q fever ongoing infection in a herd [11]. Although herd size and composition of the herd does not affect epidemiology of a herd, herd density is considered as important contribution in transmission of the disease within and out inside of the herd [11]. The organism is shed through birth products, vaginal fluids, urine, feces, and milk After calving or parturition [11,12]. *Coxiella burnetti* shed sporadically in feces and 50% of infected cows excrete the organism through vaginal fluid intermittently [8]. And 40% of onfected cows cows have excreted the bacterium through milk sporadically [8]. The organism can be excreted throughout the lactating period in cattle [13]. Importantly, the organism is persisted in a herd without having any clinical gnsigns in cattle for long period [9]. The organism is survived inan outside environment for a quite long time in a resistant spore-like form although the exact mechanism is not known [6]. Importantly, Q fever has not been reported in pigs [2].

In companion animals, cats are considered as the main source of human infection comparing to dogs. The bacterium had been isolated from feline vaginal mucosa and associated with reproductive disorders including abortion in cats [2]. No report of outbreak associated with dogs in the literature while role of canine as a reservoir of *Coxiella burnetii* is still needed to be explained [2].

It has been considered that inhalation is the main source of transmission both in animals and human, infective material are infected through inhalation [11]. Other possible methods of infection such as ingestion and vertical transmission vehave been suspected with a lack of proven evidence [11]. The organism is considered highly resistant in a farming environment and the bacterium had been isolated 2 years of post-infection in some dairy farms. In addition, *Coxiella burneitti* has been isolated from a slurry, aerosol, and dust of infective premises where infected animals were located [11]. The organism is suspected of transmission through wind and healthy farms can be infected when favorable environmental conditions are found. According to a study done at farm premises and urban environment with massive environment sampling in USA, 23.8% of samples were positive for Q fever with an

alarming risk of emerging infection to humans where who live and work in livestock farming premises [11]. Introduction of new animals with unknown history, rearing sheep/goats together with cattle was considered as a risk factor for Q fever while both negative and positive results were found with herd size [4]. Furthermore, cleaning bedding material negative effects on introduction of Q fever in a herd of cattle in the Netherlands [4].

High seroprevalence has reported in some countries such as in Belgium where prevalence of Q fever was 56.7% [8]. The prevalence of disease at individual and herd levels in France was 20% to 38% in cattle and 15% and 25% in sheep and goats [13]. In addition, in some parts of the Spain, sero prevalence was 20% while high prevalence was found in dairy animals than beef cattle [9]. Furthermore, seroprevalence was high as 79% in 2007 in the Netherlands [4]. While 18.8% of excretion in the Netherlands in 2014 [4]. In summary, either seroprevalence or prevalence of identification of genetic material such as DNA is varied with geographical location while global prevalence is varied between 4.4 to 100% from country to country and herd to herd in cattle based on bulk milk tank analysis [4]. In USA, herd prevalence of Q fever was varied from 26.3% to 94.3% in 2002 and it was 16.7 %and 5.4% in 2011, Asia [4]. Apart from the changes in seroprevalences, high genetic diversity was reported in *Coxiella burnetti* isolates from animals, farm premisses, and environment in Spain [5]. Importantly, some female sheep had been identified with excretion of the bacterium and no seroconversion by ELISA [10].

## 2.2 Zoonotic Infections

Over 3500 human cases were reported in 2007 in the Netherland with 7 deaths *by Coxiella burnetti* [13]. In human, the infection often asymptomatic and both acute and chronic infection has been reported previously (3,8]. In acute infections, flu-like infections, pneumonia, and hepatitis were observed. Chronic fatigues, endocarditis, abortion, stillbirth, and premature deliveries, were reported as chronic infections in humans [3]. Most human infections were noticed as self-limiting influenza-like illness [2]. Although mild pneumonia was common with *Coxiella burnetti*, however, the disease had been progressed to acute distress syndrome in humans [2]. In Japan, 39.7% of patients were infected with *Coxiella burnetti* [2]. Abortions, intrauterine growth retardation, fetal and neonatal death, oligoamnios, or premature delivery also were observed in infected pregnant women [2]. However, other clinical signs and symptoms were sporadic as osteomyelitis, septic arthritis, pericarditis, myocarditis, arthritis, hemolytic anemia, granulomatous hepatitis, lymphadenopathy, Guillain- Barré, optic neuritis, paralysis of the oculomotor nerve, meningitis, encephalitis, polyradiculonevritis, peripheral neuropathy, cranial nerve deficiency, and exanthema in human patients [2]. The main sources of infection in humans were from ruminants such as cattle, goats, and sheep [3]. The human disease was first reported in abattoir workers in Australia [8]. Q fever may be found in population where people consume more raw milk than pasteurized milk [2]. In Japan, most clinical cases were reported among young children, and main source of infection through cats instead of ruminates [2]. Although, person to person transmission has been reported in contact with infected or parturient women and related to blood transfusion, horizontal transmission of the disease is considered as minor importance in human [6]. Most of clinical cases reported among immunocompromised population, abattoir workers, farm workers and people who have close association with animals [6]. However, prognosis is good in human when early diagnosis of clinical infections and mortality was less than 5% [6].

Fluoroquinolone was recommended only for meningoencephalitis and other human cases were treated with doxycycline, trimethoprim-sulfamethoxazole, and hydroxychloroquine [6]. A wWhole-cell formalin-inactivated vaccine is recommended for humans while chloroform-methanol residue extracted vaccines are used in animals to control the infection [6]. However, pregnant women were shown high morbidity and mortality with further complications [6]. The seroprevalence of Q fever among veterinarians and veterinary support staff aswas 19% in Australia [14]. Vaccination with Phase I vaccine was proven results on developing clinical disease although side effect was reported on people who exposed to the organism previously [5].

### 2.2.1 Immunity and cellular defense mechanism

*Coxiella burnetti* is survived in adipose tissue and placental tissue in a host while exact survival mechanism of the organism is not unknown [15]. The bacterium invades different phagocytic cells such as macrophages and monocytes by several

mechanisms (15,5]. The *Coxiella burnetti* needs to be survived within host cell against cellular protection mechanisms to have a clinical or subclinical infection. However, some mechanisms have been described in the scientific literature such as inhibition of integrin interplay, exhibiting M1 polarizing type response, production of interleukin 10, up to taking of apoptosis cells, and unknown mechanism of regulatory T cells [15].

Although, a several studies have been carried out to understand the evading mechanism of the organism against innate immune response, only a few pieces of information are found so far [5]. Both humoral and cell-mediated immune mechanisms were recognized as an essential tool to protect against *Coxiella burbetti* infection in animals and humans [5]. Although researchers believe that, only cell-mediated immune systems have a role against intracellular parasites, antibody-mediated defense mechanisms also run an important contribution in*Coxiella burnetti* infection both in humans and animals [5]. Antibody-mediated antibody response has been shown to triggering effects on cellular defense mechanisms such as direct bactericidal activity, complement activation, opsonization, cellular activation via Fc or complement receptors, and antibody-dependent cellular cytotoxicity against *Coxiella burnetti* [5]. Furthermore, Antibodies have the role in immunoregulation on T cells' immunity against intracellular pathogen [5]. The antibody-mediated immune response in *Coxiella burnetti* is rather complexed, further extensive studies are required to understand the exact mechanisms of resistance [5]. Importantly, an infection or vaccine, both mechanism leads developing cell mediated immune response against *Coxiella burnetti* [5]. According to the current understanding, cell mediated immune response is critically important against an intracellular pathogen such as *Coxiella burnetti* [5]. T cells mediated host defense mechanism has not been fully understood, however, more studies are required to understand the exact mechanism against a clinical infection of Q fever [5].

## 2.3 Pathogenesis of Q fever

Exact pathogenesis has not been fully understood with limited information published in the literature. Multifactorial involvement are shown in pathogenesis of Q fever in which is the whole process is not limited to few virulence mechanisms [16]. The cellular invasion commenced with formation of replication-permissive *Coxiella*-containing vacuoles [16]. Then, a range of effector proteins are secreted into the host cells to react against inflammatory response [16]. Conversely, an infective dose of Q fever was low as a single organism in human and the incubation period is varied 2-6 weeks post-exposure [16]. In addition, some pathotypes of *Coxiella burnetti* were shown high virulence causing clinical infection in human and animals [6,5,16]. Therefore, genetic related pathotypes differences and host associated factors of known and unknown were involved in pathogenesis of Q fever in human and animal.

At a cellular level, *Coxiella burnetti* targets alveolar macrophages enters these cells by actin-dependent phagocytosis [16]. It has been shown that, the organism is used active trigger mechanism to induce uptake followed by attached to the surface of host cells [16]. In contrast, novel findings suggested that passive actin-dependent phagocytosis in phagocyte cells and active zipper mechanism in nonphagocytic cells in a host [16]. *Coxiella burnetti* binds macrophages through $\alpha_V\beta_3$ integrin which activates the phagocytosis on actine dependent mechanism to form Coxiella containing vacuoles [16]. These vacuoles are expanded to form large vacuoles in accordance with number of proteins described previously [16]. A few cell models to understand the pathogenesis has been developed such as mouse fibroblasts (L929), African green monkey kidney cells (Vero), human monocytes (THP-1), and mouse macrophages (J774) [6,16].

## 2.4 Diagnostic Test

The bacterium can be detected in different clinical samples such as milk, vaginal mucous, feces, urine, semen, birth fluid, and placental membranes [8]. Identification of the bacterium can be done by conventional bacteriological methods; molecular methods and detection of antibodies were done by serological methods such as ELISA [17]. Identification of the organism and serological diagnosis in bulk milk tanks is the most practical way of diagnosis in ruminants [17]. Serological diagnosis is considered to be a gold standard of diagnosis of Q fever in humans [17]. In human diagnostic methods inlcuding, IFA, CFT, and ELISA are used widely for serological diagnosis of the disease [2] Furthermore, qPCR methods are highly sensitive to detect the organism in clinical samples with high accuracy [2]. Sampling is a vitally important step in

identification of *Coxiella burnetti* in the clinical specimens [6,2]. A collection of samples avoiding contamination is critical such as cleaning of teats with ethanol or chlorhexidine di-gluconate is recommended [6]. Similar practice is recommended to vaginal swabs in order to increase sensitivity and accuracy of the diagnostic tests.

#### 2.4.1 Control or eradication of the infections and vaccination

Antibiotics treatment, vaccination, and a combination of these two are the possible alternative to control clinical disease in cattle [12]. Mainly antimicrobials such as tetracycline are used at the beginning ofa dry period and around calving to prevent abortion and excretion of *Coxiella burnetti* in milk respectively [12]. However, some of the literature reported that antimicrobial therapy with tetracycline with no results on reduction of excretion or bacterial load in cattle herd [18]. Therefore, a combination of screening of herd and vaccination was recommended to control *Coxiella burnetti* in ruminants [11]. In addition, tick control in the farm is considered an important measurement to reduce the risk of an animal.

### 2.5 Vaccination

A few vaccine types have been recognized and used in human and animal to control *Coxiella burnetti* infections such as inactivated PI or PII, attenuated PII *Coxiella burnetii* and a chloroform: methanol residue fraction of Nine Mile phase I vaccine is used in the field which is killed vaccine and used to control the excretion of the organism in sheep/goat and cattle [5]. In sheep, it has been observed that no excretion of the organism in ewes and yearling for two years of post-vaccination by Phase I vaccine [19]. However, excretion of the bacterium was decreased in vaccinated cattle with phase I vaccine by reducing a number of shedders in a herd and reducing bacterial load shed [18]. The difference between Phase I and II vaccines was presence of LPS core polysaccharides O side chain expression in phase I organisms which are require forfor development of immunity [5]. In addition, reduction of bacterial load was observed in many routes of excretion while vaccination or healthy or *Coxiella burnetti* free cattle were shown good results comparing to infected animal although excretion was reduced [18]. Furthermore, at least 80% of animals at herd were given satisfactory results on reducing the bacterial load and percentage of excretion in cattle [18]. Vaccination of goats resulted in decreasing excretion of the organism in milk with phase I vaccine in Netherlands [11]. Multiple vaccinations had reduced excretion of the organism in milk from goat farms [11]. In humans, inactivated vaccines gave satisfactory results to control the clinical infection of *Coxiella burnetti*. However adverse reaction had been observed, a whole-cell vaccine has been developed with low adverse reaction and good immunogenicity. A subunit vaccine is still working on on the research basis in humans [5].

## 3. CONCLUSION

*Coxiella burnetti* is an important pathogen in ruminants, potential risk of zoonotic trasnsmisions is still going on in both developed and developing counntries. Although wide gap is still exist in pathogenesis and immunity, the vaccination is the main way of controlling Q fever in ruminats and pssible minimizing zoonotic infection. Control and eradication of disease in ruminat may be the solution of preventing Q fever in human. However, no report has been found or published on Q fever among ruminants in Sri Lanka.

## ACKNOWLEDGEMENT

Author would like to acknowledge the Fleming Fund, UK and University of Hong Kong for the providing facilities to read and download relevant literature.

## COMPETING INTERESTS

Author has declared that no competing interests exist.

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*The peer review history for this paper can be accessed here:*
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