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Review Article

Q-Fever, an undermined zoonotic threat

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ABSTRACT

With upto 75% of all human disease being zoonotic in origin, proper study of the diseases is necessary to prevent any outbreak or human loss. More studies are required for developing countries like Nepal where there are no appropriate provisions for situations after breakouts. One such little known sporadic zoonosis is Q-fever. Q-fever (Coxiellosis) is caused by Gram-negative bacterium *Coxiella burnetii* that infect cattle and other ruminants with serious concerns for developing reproductive disorders and flu-like symptoms in human. There have been reports of undifferentiated febrile illness of Rickettsial cause in human and seroprevalence of Coxiella antibodies in goats of Chitwan and dairy cattle of Rupandehi for the first time. Low infectious dose and high resistivity to environment makes the disease more potent. Q-fever continues to be unexplored in Nepal despite its identification in neighboring countries like India. Thus, this paper after reviewing related articles from various journals, proceedings and magazines from online sources like Google Scholar, Mendeley, NCBI and PubMed is aimed to evaluate current status of disease, its epidemiology, zoonotic potential and preventive measures that can be adopted to minimize the threat of the disease as much as possible.

Keywords: Coxiellosis, Q-fever, Rickettsia, Zoonosis

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INTRODUCTION

Q fever is an important zoonotic bacterial disease with great public health significance worldwide. Q fever (for query fever), is a zoonosis due to *Coxiella burnetii*, an obligate Gram-negative, non-motile intracellular bacteria (Honarmand, 2012). The disease has been recognized since the 1930s and has global distribution, with the exception of the Antarctica and perhaps New Zealand (Hilbink *et al*, 1993), where its presence has not really been confirmed (Greenslade *et al*, 2003).

The 'Q' stands for 'query', the name being given since the explanation of a 1935 outbreak of illness among abattoir workers in Australia was unknown. The microorganism of Q fever was discovered in 1937, once Frank Macfarlane Burnet and Mavis Freeman isolated the bacterium from one of Derrick's patients (Burnet & Freeman, 1937). It was once firstly recognized as a species of *Rickettsia* by H.R. Cox and Gordon Davis from ticks in Montana, USA in 1938 (Davis & Cox, 1938). Q fever was first delineated by Edward Holbrook Derrick (Derrick, 1983) in abattoir workers in Brisbane, Queensland, Australia. Patients were presented with fever, headache and malaise. Serological tests for various possible etiologic agents were negative. Due to the unknown etiology, the term Q fever was so given for query (Maurin & Raoult, 1999). As is frequently in the nomenclature of microorganisms, there has been a collection of name for this agent. Initially, *R. diaporica* to *R. burnetii* and was later elevated to subgenus, *Coxiella* on the basis of cultural and biochemical characteristics. The agent is now known as *Coxiella burnetii* (Marrie, 1990). The name thus given is to honor two scientists; H.R. Cox and F.M. Burnet.

The disease is a highly contagious zoonosis present in virtually all 'animal kingdoms', including arthropods; affects mostly humans, cattle, sheep and goats (Arricau-Bouvery & Rodolakis, 2005; EFSA, 2010; Lang, 1990; Maurin & Raoult, 1999). The foremost reservoir for the infective agent are domestic ruminants like cattle, sheep and goats while it can infect a large range of hosts such as mammals (humans, ruminants, small rodents, dogs and cats) and additionally birds, fish, reptiles and arthropods (Porter *et al*., 2011). *C. burnetii* is extremely infectious, and solely few organisms can cause disease. It will stay viable and virulent for months due to its spore-like life cycle. (Honarmand, 2012).

Humans typically get the infection through contaminated dust or by direct contact with infected animals or while aiding with the delivery of newborn animals, and infrequently by drinking contaminated milk or from tick bites. Affected persons develop high fever with headache, muscle pains, sore throat, nausea, vomition, chills, night sweats, fatigue, chest pains and stomach pains. In serious cases, it can lead to pneumonia and hepatitis. Q fever is an occupational hazard with farmers, veterinarians, abattoir workers, workers in dairy industry and laboratory personnel being at risk (Maurin *et al.*, 1999). Despite Q fever being an OIE notifiable disease, it remains poorly reported and its surveillance is severely neglected (Porter *et al*., 2011).

C. burnetii is taken into account as a weapon for bioterrorism, as the infectious dose of *Coxiella burnetii* is possibly one rickettsia and a single organism is sufficient to cause infection (Waag,

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2007), with probability being approximately 0.9 (Jones *et al.,* 2006). The infectious particle is extremely resistant to environmental degradation. Because of its high infectivity and stability in the environment, *C. burnetii* is listed as a Category B biothreat agent. (Waag D. M., 2007). According to Brooke *et al.* (2013), the dose for 50% infection (InfD50%) in human subjects is 1.18 bacteria; dose for 50% illness (IllD50) in challenged humans is 5.58 bacteria. Also, the probability of a single viable *C. burnetii* causing infection in humans is 0.44 and for illness 0.12.

METHODOLOGY

In order to identify all published articles on Q fever, a systematic literature search was conducted in PubMed, NCBI, Mendeley, Google Scholar and NARC online library. Journals and thesis found in the library of IAAS was also taken for primary information. Searches were restricted to English language only. Keywords such as 'Q fever', 'Coxiellosis' and 'Zoonosis', their synonyms and closely associated words were used for the search. Also, references cited in the included studies were utilized for possible relevance.

RESULTS AND DISCUSSION

Etiological agent

Q fever is caused by an obligate intracellular, small, Gram-negative coccobaillus bacterium *Coxiella burnetii* (0.2 to 0.4µm wide, 0.4 to 1µm long). Although possessing a membrane comparable to that of a gram-negative bacterium, it is typically not stainable by the Gram technique. Gimenez method is usually used to stain *C. burnetii* in clinical specimens or laboratory cultures (Eldin *et al.*, 2017). Although classically viewed a rickettsial agent, recent phylogenetic analyses advocate that *C. burnetii* is more closely associated with *Legionella* and *Francisella* than to the genus *Rickettsia*. (Plummer, 2015). To date based on 16S rRNA sequence analysis, the bacterium was reclassified from the order Rickettsiales to Legionellales and falls in the gamma group of Proteobacteria (Angelakis & Raoult, 2010).

Unlike rickettsiae, *C. burnetii* produces a small, dense, highly resistant spore-like form that is highly stable in the environment (Gwida, 2012). It can survive for 7-10 months on walls at 15-20^0C, for more than 1 month in cold storage and for more than 40 months in skim milk at room temperature (Angelakis & Raoult, 2010). The survivability has been attributed to the existence of *C. burnetii* developmental cycle variations; large-cell variants (LCV), small-cell variants (SCV) and small dense cells (SDC) (Coleman *et al.,* 2004). SDC and SCV can likely survive extracellularly as infectious particles even in extreme environmental conditions (Gwida, 2012). LCVs are metabolically active cells that undergo differentiation to produce resistant spore-like forms, the small-cell variants. These are released when the cells lyse and can survive for long periods in the environment (Angelakis & Raoult, 2010).

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Epidemiology

Q-fever is established zoonotic disease worldwide listed in OIE Terrestrial Animal Health Code. Low infectious dose and ability of its spore to withstand harsh environmental conditions makes the disease present constantly around. The sickness was first reported in 1935 in abattoir workers

in Brisbane, Australia as outbreak of febrile illness (Derrick, 1953). The disease is endemic, occurring in numerous geographic regions and climatic zones (Marrie, 1990).

Host Distribution

The epidemiology of *C. burnetii* is complex due to the fact that it has two major patterns of transmission. The organism circulates between wild animals and their ectoparasites, primarily ticks and alternative one occurs in domestic ruminants independent of wild animal cycle (Plummer, 2015). Cattle, sheep and goats are the most important reservoirs for human infections though it is found in a wide range of hosts. Horses, pigs, dogs, cats, camels and buffaloes and wild and domestic birds such as chickens, pigeons, ducks, geese and turkeys can be infected without showing any clinical signs (Acharya, 2015). Pets such as rabbits, dogs and cats have been known as potential source of urban outbreaks (Langley *et al.,* 1988).

Geographic Distribution

Q fever has been described in the world all over except in New Zealand. There were 18 recorded outbreaks of Q fever from 12 different countries from 1999 to 2004 with 2 to 289 people involved (Arricau-Bouvery & Rodolakis, 2005).

Incidence in the Netherlands:

Q fever outbreak has been ongoing in The Netherlands since 2007 with the largest Q fever outbreak ever mentioned with more than 4000 reported cases and an rumored estimate of more than 40,000 total cases (Schneeberger *et al.,* 2014). Q fever was made notifiable in The Netherlands in 1975 when it used to be very rare and new to other countries. The annual increment of cases were seen from 0 to 32 per year between 1975 and 2006 (Roest *et al.,* 2011).

Incidence in England and Wales:

From 1975 to 1995, 67 to 169 Q fever cases were reportable yearly to the Communicable Disease Surveillance Center by laboratories in England and Wales (Maurin *et al.,* 1999). 904 cases of acute Q fever were reported in England and Wales between 2000 and 2015 that corresponds to mean annual incidence of 0.09 cases/100,000 populations/year without considering outbreak cases (Halsby *et al.,* 2017).

Incidence in Switzerland:

Only 30 to 90 Q fever cases are reported annually to the Federal Office of Public Health in Switzerland (Maurin *et al.,* 1999). In a large outbreak in 1983, 191 patients seen in the cases reported from the end of October to the beginning of December 1983 were serologically confirmed as acute Q fever by Complement Fixation and Indirect microimmunofloroscence test (Dupuis *et al.,* 1987).

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Incidence in USA:
The prevalence of *C. burnetii* is poorly reviewed in United States. The first major Q fever outbreaks was reported in 1946 (Maurin *et al.*, 1999). Q fever became notifiable disease in United States in 1999. The cases have increased from 21 cases per year (1978-1999) to 51 cases per year (2000-2004) (Hartzell *et al*., 2008).

Incidence in Bhutan:
15.2% of the patients presented with an undifferentiated febrile illness in 14 hospitals during the study period had evidence of concurrent rickettsial infection with maximum case of scrub typhus followed by Q fever (2.8%) (Tshokey *et al.*, 2018).
Incidence in India:
In research conducted in India, the overall prevalence of Q fever in animals with history of reproductive disorder was seen to be 13.82%. The species-wise variation of prevalence of Q fever was observed to be 12.78% in cattle, 16.66% in buffaloes, 11.04% in sheep and 6.13% in goats (Vaidya *et al.*, 2010).

Transmission

The most common mode of transmission of *C. burnetii* is through ticks (Angelakis & Raoult, 2010). *C. burnetii* may infect around 40 species of ticks. Ticks are the reservoirs and vector of transmission to domestic mammals but not to humans (Chakrabarti, 2012). The organism is easily excreted in milk, urine, faeces and parturition products (amniotic fluid, placenta) of affected cattle, sheep, goats and other ungulates. Ingestion of contaminated products and inhalation of airborne contaminants are other ways of development of the disease. Close contact with the infected animals or with body fluids or secretions also results in the disease. Significant number of livestock handlers are proven to have antibodies against Q fever indicating exposure to the organism. Hence, Q fever is classified as occupational disease.

Reservoirs

Coxiella burnetii has wide range of reservoirs that encompass mammals, birds, and arthropods, mainly ticks. The common identified source of human contagion are farm animals such as cattle, goat and sheep. Although over 40 species of tick can be naturally infected with *C. burnetii*, they appear of no importance in maintenance of infections in livestock or humans(Maurin *et al.*, 1999). The organism multiplies in the gut cells of ticks and large numbers of *C. burnetii* are shed in tick faeces. In domestic ruminants, Q fever is mostly associated with abortions and dead or weak offspring. The infection is probably life-long or persisting for several years. Sheep, goats and cows are principally subclinical carriers, however can shed bacteria in their secretions and excreta.

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Q Fever in animals

Coxiella burnetii can infect wide range of animal species including farm animals (Gwida, 2012; Marrie, 1990). Infections in animals usually go unnoticed without developing any significant signs and symptoms. Reproductive failure is usually the only symptom presented when clinical disease occurs.*C. burnetii* are seen lodged in uterus and mammary glands of infected animals. The initial signs of the disease are anorexia and high rise of temperature. Abortion, stillbirth, premature delivery and delivery of weak offspring are commonly manifestation in ruminants (Angelakis& Raoult, 2010). Anorexia and abortions have been reported more frequently in sheep and goats (Gwida, 2012). Abortion occurs at later stage of pregnancy with no any apparent signs of abortion. The abortion rate ranges from 3 to 8%. Aborted females used to recover quickly but does not abort in the next gestation usually (Chakrabarti, 2012). On the basis of epidemiological data, dairy cows are more infected than sheep and goat which represent the vital source of human infection (Gwida, 2012).

Significance and impact on public health

Humans are the only species developing symptoms of the disease ranging from acute to chronic signs. Q fever is essentially air-borne disease with infection occurring after inhalation of contaminated aerosol. The infectious dose of *Coxiella burnetii* is possibly one rickettsia and the chance of a single organism initiating infection is approximately 0.9 (Jones *et. al.,* 2016). The primary attribute of Q fever in humans is its clinical polymorphism (Derrick, 1953). After incubation period of 1 to 3 weeks, the disease may progress to either acute or chronic phase.

Acute Q fever

50 to 60% of cases can be completely asymptomatic in the acute form or show illness associated with fever, fatigue, headache and myalgia (Porter *et al.*, 2011). Acute Q fever has no typical form. The clinical signs vary in each patient but three main clinical presentations are- flu-like syndrome, pneumonia and hepatitis. The self-limited febrile illness with flu-like symptoms is characterized by a sudden onset of high-grade fever reaching 40^0C, severe headache, weight loss, myalgia and cough(Maurin et al., 1999).

Atypical pneumonia is most commonly recognized form of acute Q fever. It is characterized by non-productive cough, fever and minimal auscultatory abnormalities but some patients are present with acute respiratory distress. Pleural effusions can be present but findings on the chest radiograph are nonspecific. (Honarmand, 2012). Acute Q fever is found primarily as a granulomatous hepatitis. However, in patients infected by aerosol route, Q fever is more common (Gwida, 2012).

Cardiac involvement is seen in 2% of the acute Q fever cases where myocarditis is the leading cause of death. In the study, patients with valvular diseases who experience acute Q fever may remain asymptomatically infected. (Fenollar *et al.*, 2002). Some other clinical manifestations are meningoencephalitis, lymphocytic meningitis, peripheral neuropathy, fatigue, rigors, night sweats, vomiting, pancreatitis and abortion.

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Chronic Q fever

According to Arricau-Bouvery and Rodolakis (2005) approximately 5% of acutely ill patients are reported have chronic form. It may develop many months to years after infection. The major manifestation of acute form is endocarditis. Incessant Q fever happens only in patients with inclining conditions incorporating those with heart valve sores, vascular anomalies and immunosuppression (Fenollar *et al.*, 2002). The most common symptoms relate to heart and circulatory impairment due to endocarditis in 60-70% of cases. Other conditions associated with chronic Q fever embody osteoarticular infections and continual pulmonary infections. In addition to circulatory effects, chronic hepatitis is another common feature as is persistent fatigue syndrome (Wildman *et al*., 2002).

Pregnant Women

Both acute and chronic Q fever have been described during pregnancy. *C. burnetii* undergoes reactivation in the course of pregnancy and thus is accountable for higher rates of abortion, prematurity and low birth weight(Zeman *et al*., 1989). The risk is greater in the first trimester for pregnant women. In human, it has been isolated from the placenta of a woman who became pregnant 2 years after the episode of acute Q fever (Prasad *et al*., 1986), but few cases have been reported. Intrauterine transmission of *C. burnetii* has been pronounced but the consequences of congenital Q fever is yet to be determined (Honarmand, 2012).

Scenario of Q-Fever in Nepal

Undifferentiated febrile illnesses(UFIs) are a common clinical problem in south Asia (Chrispal *et al.*, 2010). These are the fever barring a focus of infection on initial physical examination or in simple laboratory tests. In a study of UFIs in 627 patients from July 2008 to August 2011, serological evidence of *Rickettsia* was found to be 57% with one UFI case seropositive for Q fever (Thompson *et al*., 2015). Seropositivity in domestic animals have been recently detected in Nepal. The overall seroprevalence rate was found to be 1.45% (3.03% in sheep and 0% in goat) among 276 serum samples of goat and sheep in Bardiya and Surkhet district, Nepal (Koirala, 2015), while 10% of 100 serum samples from goats with history of abortion and still births were seropositive in Chitwan district, Nepal (Acharya, 2015).This was the first instant of seropositivity of Coxiellosis detected in goats of Nepal (Acharya, 2015).In another study from October 2016 to December 2016, 1.63% of dairy cattle was reported to have circulating antibodies against *C. burnetii* in their blood (Panth et al., 2017). This was also Nepal's first moment of seropositivity in cattle.

The disease is new and yet unknown to many concerned authorities in Nepal. The government sector is all focused and prioritized on the prevalent zoonosis and economic disease like FMD, Brucellosis, Mastitis, etc. in the livestock sector at the moment. There is primary import of goats and other livestock from India associated with limited quarantine health assessment for Q fever. In such context, it is the next zoonotic disease waiting for the golden opportunity of breakout. Seroprevalence of the disease all over Nepal must be done within few years so that we can

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determine the exact status of Q fever in Nepal. Once the disease status is known, the way forward can be planned accordingly. But there must be strict quarantine measures with assessment of Q fever as a must so that we can prevent the disease from entering the territory rather than to control after its emergence.

Prevention and control

Sanitary and prophylactic measures ought to be applied at herd and human level so as to minimize disease transmission at the time of Q fever outbreak. Measures to avoid exposure between human and persons at risk, animal and environmental contaminant should be followed. Regular cleaning and disinfection reduce the number of *C. burnetii* in the farm environment.

Although vaccines for Q fever are developed, no vaccines have been permitted for use by the Food and Drug Administration(Hartzell *et al.*, 2008). In field trials C. burnetii vaccines of inactivated whole cells (WC) in phase (ph) I as well as WC ph II vaccines prevented infections of cows exposed to naturally infected environments, provided they were vaccinated as non-infected calves (Schmeer *et. al*., 1987). Q-Vax has been licensed for use in Australia, as part of a preventive vaccine program, highlighting an important success by effectively reducing the disease burden (Ruize & Wolfe, 2014).

Finally, it is important to recollect that *C. burnetii* is extremely hazardous to humans and laboratory infections are frequent. Its low infectious dose, resistance in environment and aerosol route of transmission makes it fatal and protracted once after outbreak. *C. burnetii* is considered a potential agent of bioterrorism and is classified by the CDC as a group B agent. Live culture or contaminated material should be handled in proper facilities (Gwida, 2012).

CONCLUSION

There have already been reported cases of Q-fever in Nepal and many reports of undifferentiated febrile illness of Rickettsial nature. With positive seroprevalence in carriers and reports of outbreak in neighboring countries, Q-fever is next zoonosis looming over us that can strike at any instant. As we lack preparations for aftermath situations, we must have knowledge on prevention measure of the disease to limit its impact. The researches accomplished in Nepal have few sample sizes, so the validity and accuracy of this research could be challenged through increased sample sizes. Enhanced surveillance using confirmatory techniques with sufficient sample size is a prerequisite to confirm the findings. Further epizootiological investigations on Q fever in other farm animals and man at the country level is important to monitor and determine the magnitude of Q fever infection in order to estimate its economic impact on animal industry and its public health hazard.

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Author Contributions

SPS conceived the original paper. YP extensively revised and provided his inputs. KK and SPS provided their feedback. All authors got final approval of revised version to be published.

Conflicts of Interest

The author declares that there are no conflicts of interest.

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