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Review
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Q fever, a neglected zoonotic disease in Nigeria- a review

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ABSTRACT

Q fever still remains a neglected zoonotic disease in several developing countries including Nigeria. The aetiologic agent *Coxiella burnetii* is a resistant intracellular bacterium which causes long-lasting infections in both human and animals. The infection is usually asymptomatic in animals but can affect reproduction such as abortion in animal herds resulting in the disease mostly remaining undiagnosed leading to economic consequences. In humans, the infection can lead to severe endocarditis and vascular infection in chronic cases. Data is still limited on the molecular epidemiology such as genomic studies and evolution of this pathogen especially in humans and this has to be explored. Awareness programs on the public health importance of this disease, it's preventive and control measures in Nigeria would help in Q fever management.

KeyWords: *Coxiella burnetii*, Nigeria, Q fever , zoonosis,

INTRODUCTION

Query fever also known as Q fever is a zoonotic disease caused by *Coxiella burnetii*, an intracellular, obligate gram-negative bacterium. The name "Q fever" originated from "Query fever" when the disease was first described in 1935 in Queensland, Australia where there was an outbreak of a febrile illness (Query fever) with flu-like symptoms among abattoir workers (Porter *et al.,* 2011). It occurs worldwide except in the Netherlands and it is transmitted to humans through direct contact with milk, urine, feces or semen from infected animals as well as through the inhalation of aerosolized particles from animal placentas, aborted fetuses and environmental dust (Tissot-Dupont & Raoult, 2008; Honarmand, 2012). Rare human-to-human transmissions occurs involving exposure to the placenta of an infected woman and blood transfusions (Cutler *et al.,* 2007). Cases of sexual transmission have also been reported (Domingo *et al*., 1999).

Coxiella burnetii has a wide host range; they include wild and domestic mammals, birds, reptiles, and arthropods with goats, cattle, and sheep representing the most frequent source of human infection (Maurin & Raoult, 1999; Honarmand, 2012). In female animals, the uterus and mammary glands are the sites of chronic infection and can shed the bacteria into the environment following abortion or during parturition. *Coxiella burnetii* is highly infectious, such that only a few organisms can cause disease. Because of its spore-like life cycle, *C. burnetii* can remain viable and virulent in the environment for several months (Maurin & Raoult, 1999).

Coxiella burnetii infection in humans can be asymptomatic or a symptomatic infection known as Q fever. Q fever can present as an acute febrile illness that can have focal manifestations such as hepatitis and pneumonia. The acute disease can progress to chronic forms such as endocarditis especially in patients with preexisting valvular heart disease (Brouqui *et al.,* 1993;Tissot-Dupont *et al.,* 2007; Van der Hoek *et al*., 2011). *Coxiella burnetii* infection in livestock species is often asymptomatic but it can cause abortion and reduced reproductive efficiency (Tissot-Dupont & Raoult, 2008; Angelakis and Raoult, 2010). Because of its highly infectious nature and having an inhalational route of transmission, *C. burnetii* is recognized as a potential agent of bioterrorism (Honarmand, 2012).

METHODOLOGY

Relevant publications were obtained from online databases using PubMed and Google Scholar search engines from March- May, 2023. For the search, the following descriptors were used either in isolation or combined: "*C. burnetii*", "Q fever", "zoonosis", "neglected" and "Nigeria".

The inclusion criteria for publications included relevance to the topic with complete and verifiable referencing. Exclusion criteria included publications that were without references,

inadequate referencing, obsolete references, irrelevant topics, unverifiable information and duplicate information. Following the literature search, 30 articles were obtained and 13 were used for the review of which 6 were review articles and 7 were research articles. These were the major articles used to develop the content of this review, though some other papers cited by these 13 were also consulted for further detailed understanding of the subject matter.

AETIOLOGY

Coxiella burnetii is a gram negative, obligate intracellular, pleomorphic bacterium about 0.2 to 0.4μm wide and 0.4 to 1μm long (Ullah *et al.,* 2022). *Coxiella burnetii* has been classified in the *Rickettsiales* order, of the *Rickettsiaceae* family because it has been recovered from ticks (Ullah *et al.,* 2022). The incubation period in humans varies from 2-4 weeks or more and depends largely on the route of infection, inoculation dose and the antigenic phase. A unique characteristic of *C. burnetii* is it possesses an antigenically distinctive lipopolysaccharide (LPS) molecule in its cell wall which exists in two forms:, Phase -I and Phase- II (Abnave *et al*., 2017).

Phase I is the natural phase found in infected animals, arthropods, or humans. It is highly infectious and corresponds to smooth LPS (Honarmand, 2012). In contrast, phase II is not very infectious and is obtained only in laboratories after serial passages in cell cultures or embryonated egg cultures. Currently, available commercial tests allow the detection of at least the anti-*C.burnetii* phase II antibodies, which appear to be present at whatever the infection stage or form. In contrast, vaccination is effective with a phase I vaccine but not with a phase II vaccine (Honarmand, 2012).

EPIDEMIOLOGY

Q fever has been described as a worldwide zoonosis except in New Zealand (Cadmus *et al.,* 2021). The reservoirs are extensive but only partially known and they include mammals, birds and arthropods, mainly ticks (Honarmand, 2012). Over 40 tick species can be naturally infected with *C. burnetii* and the ticks seem to be important in the maintenance of infections in livestock or humans (Maurin and Raoult, 1999). While the important reservoir seems to be small wild rodents, the most commonly identified sources of human infection are farm animals such as cattle, goats, and sheep (Honarmand, 2012). Some pets which include cats, rabbits, and dogs, have also been demonstrated to be potential sources of outbreaks in the urban areas (Higgins and Marrie, 1990). Infected mammals shed the organism in urine, feces, milk and most especially in birth products (Kazar, 1996). In female animals, reactivation of the infection is said to occur during pregnancy. Q fever causes abortion in goats, sheep and cattle as well other reproductive problems (Zeman *et al.,* 1989). High concentrations of *C. burnetii* are usually found in the placentas of infected animals and due to its high resistance to physical agents can survive for long periods in the environment (Honarmand, 2012).

In humans, infection usually results from the inhalation of contaminated aerosols from amniotic fluids, the placenta or contaminated wool. Consumption of raw milk can also be a source of infection as infected mammals also shed *C. burnetii* in milk while sexual transmission has been suspected (Tissot-Dupont & Raoult, 2008).Q fever is said to be an occupational hazard for persons in contact with farm animals and laboratory personnel are at the highest risk of infection (Honarmand, 2012). Other sources of infection in humans can include trans placental transmission as a result of congenital infections, intradermal inoculation and via blood transfusion (Tissot-Dupont & Raoult, 2008) .

TRANSMISSION AND CLINICAL SIGNS IN ANIMALS

Ticks are important for the maintenance of the organism in nature but are not essential vectors for animal or human infection. *Coxiella burnetii* is shed in the environment by infected animals in vaginal secretions, placenta, amniotic fluids, milk, feces, urine, saliva and other products of conception (Cadmus *et al*., 2020). In domestic animals, milk is the most common route by which the pathogen is shed. Vertical transmission and sexual transmission could also occur but their importance is not known (Nakeel *et al*., 2016). The most likely way in which animals can acquire the infection is by inhalation of the organisms from an infected environment and by the ingestion of contaminated pastures, hay, straw, etc. The well-known clinical signs of Q fever in ruminants has been associated mostly with reproductive disorders such as abortion, stillbirth, premature delivery and delivery of weak offspring (Nakeel *et al*., 2016).

In cattle, the disease can also be associated with metritis and infertility. *Coxiella burnetii* is present in very high numbers in the amniotic fluid, the placenta and foetal membranes of parturient ewes, goats and cattle and infected animals may continue to shed infectious particles into the environment long after abortion (Woldehiwet, 2004, Berri *et al*., 2007). The determination of the status of Q fever is difficult due to the lack of knowledge on the shedding patterns among ruminants (Nakeel *et al*., 2016). Within herds or flocks experiencing abortion problems caused by *C. burnetii*, most of the animals may be shedding massive numbers of bacteria whether they have aborted or not.

Several studies have demonstrated that epizootics of Q fever in goats are related to the outbreaks in humans (Rousset *et al.,* 2009). Stillbirth and the delivery of weak kids are the two most frequently seen clinical signs of Q fever in goats. Other signs include pneumonia and abortion which

principally occurs towards the end of gestation (Berri *et al.*, 2007).

Dogs and cats infected with Q fever have also been associated with human infections due to their closeness to human as pets. Infected felines are usually asymptomatic but excrete the bacteria in the environment which is a source of infection to humans (Porter *et al.,* 2011). Dogs can become infected through inhalation, tick bites, consumption of placentas or milk from infected ruminants (Porter *et al.*, 2011).

TRANSMISSION AND CLINICAL SIGNS IN HUMANS

Infection in humans occurs after the inhalation of aerosols generated from infected placenta, body fluids or contaminated dust (Terheggen & Leggat, 2006). Ingestion of contaminated food or infected unpasturized milk can also serve as a source of infection. Human to human transmission does not usually occur and sexual transmission of Q fever is said to be rare (Porter *et al*., 2011).

Coxiella burnetii can survive in the environment for long periods, with aerosols remaining infective for up to 2 weeks and contaminated soil for up to 5 months (Terheggen & Leggat, 2006). Inanimate objects (fomites) such as wool, straws, materials contaminated with infected animal excreta can serve as vehicles of transmission (Woldehiwet, 2004).

Human infection with *C. burnetii* can be either subclinical, acute or chronic (Maltezou & Raoult, 2002). Asymptomatic infection with Q fever is common since over time, the number of serologically positive persons were observed to be much higher than the incidence rate of the disease (Norlander, 2000). The incubation period of the acute infection ranges from two to four weeks. The clinical symptoms resemble those of influenza (fever, headache and myalgia) and the disease can become complicated with pneumonia and granulomatous hepatitis (Norlander, 2000). Cases of febrile eruptions, myocarditis, pericarditis and meningoencephalitis have been reported (Maltezou &Raoult, 2002). There is an indication that *C. burnetii* undergoes reactivation during pregnancy in humans as the organism has been isolated from the placenta and breast milk of mothers who have had an acute Q fever infection few years before delivery (Norlander, 2000). Chronic Q fever infection is often characterized by endocarditis which may develop after an acute infection. The development of acute or chronic Q fever infection is assumed to depend on the patient's condition and immune status rather than on specific 'acute' or 'chronic' *C. burnetii* strains (Terheggen & Leggat,2006).

DIAGNOSIS OF Q FEVER

Coxiella. burnetii is highly infectious and as a result, specimens must be handled in biosafety level 3 laboratories (Fournier *et al*., 1998). Samples that can be used for laboratory diagnosis include blood, tissue samples, uterine discharges, aborted foetuses, placenta, milk and urine (Baba *et al.,* 2023).

The diagnostic techniques that can be used for Q fever diagnosis are grouped into four categories namely; (i) isolation and propagation of the organism, which requires BSL-3 laboratory using tissue culture, embryonated chicken eggs or laboratory animals; (ii) serodiagnostic tests including Indirect Fluorescent antibody (IFA), Complement fixation test (CFT) and enzyme immunoassay; (iii) antigen detection assay such as immunohistochemical staining (IHC); and (iv) genomic detection assays such as Polymerase chain reaction (PCR). For confirmatory diagnosis, it is recommended that various laboratory tests are combined such as Enzyme-linked immunosorbent assay (ELISA) for serology and PCR for nucleic acid detection (Bontje *et al*., 2016).

Serological techniques are largely preferred in the diagnosis of Q fever since they are less expensive and laborious compared to the isolation techniques. These techniques are best used to estimate the prevalence of the infection in animals and humans and they can detect the difference in titers present in acute or chronic infection (Lucchese *et al*., 2015).

Enzyme-linked immunosorbent assay method has been endorsed by the European Food Safety Authority (EFSA) to be the most specific and sensitive technique than any of the other serological assays. For diagnosis in animals, ELISA is preferred to IFA and CFT because of its convenience for herd- or flock-level screening and its ability to detect *C. burnetii* antibodies in various animal species (Selim & Elhaig, 2016).

Polymerase chain reaction is the diagnostic technique used for the molecular detection of *C. burnetii* and it is rapid, highly specific and sensitive. The specimens that can be used for PCR include fetal membranes, fetal fluids, genital swabs or samples from aborted fetuses (liver, lung or abomasal contents). Blood, serum, milk, urine, anal and throat swab specimens are also useful for genomic detection of *C. burnetii* using qPCR (Selim & Elhaig, 2016). Polymerase chain reaction targets the insertion sequence IS1111 which is a repetitive transposon-like element of *C. burneti i*and is highly sensitive and specific for genomic detection. Following detection of seropositive animals in a flock using serological assays, the quantitative real-time PCR is then a technique of choice to trace the shedders (Niemczuk *et al.,* 2014).

RISK FACTORS ASSOCIATED WITH *COXIELLA BURNETII* INFECTION

The main reservoirs of *C. burnetii* which are responsible for human outbreaks are domestic ruminants. Therefore, it is vital that continous monitoring of *C. burnetii* infection is done in them. These reservoirs act as carriers, shedding the

bacteria in birth products, urine faeces and milk (Eldin *et al.*, 2017). As a result of this, Q fever is considered as an occupational disease since people who come in direct contact with livestock such as farmers, abbattoir workers, veterinarians, laboratory technologists cultivating the bacterium are at a higher risk of infection (Miller *et al.*, 2021).

To reduce the risk of infection in domestic ruminants, preventive farm management measures must be effected. Identification and slaughter of herds and the control of animal movements can influence transmission to humans (Souza *et al.,* 2022). In Nigeria, some of the factors associated with infection with *C. burnetii*i n ruminant herds include sources of water for the livestock, the watering system and method of handling of aborted foetuses.

PREVENTION AND CONTROL

As with all zoonotic diseases, the control of the disease in animals influences the level that is observed in humans. For appropriate control of Q fever the following measures are necessary; disease surveillance, regular monitoring, implementation of proper preventive and control measures. Components of control measures include adequate tick control strategies, the practice of proper hygiene to decrease environmental contamination and appropriate disposal of infected fetal fluids, membranes, aborted fetuses, contaminated bedding and proper treatment of manure (Angelakis & Raoult, 2010. Other preventive measures include the separation of infected and pregnant animals before parturition from herds,. Training and creating awareness among livestock-associated professionals and farmers especially with those that are occupationally at risk of acquiring Q fever are important in reducing the risk of disease spread.

These strategies are important as they pose economic and public health significance in reducing reproductive losses in the livestock industry as well as the prevention of potential risk of transmission of infection to humans (Ullah *et al*., 2022).

TREATMENT

Treatment is mainly done in humans as Q fever is usually asymptomatic in animals. In ruminants, the administration of of oxytetracycline during the last month of gestation may be done, although this treatment does not totally suppress the abortions and the shedding of *C. burnetii* at lambing (Ullah *et al*., 2022).

In humans, the drugs of choice for Q fever are doxycycline and hydroxylchloroquine. These drugs are mostly used in combination but other antibiotics, such as erythromycin, rifampin, roxithromycin and clarithromycin can be used as alternatives (Shah *et al.,* 2015; Hadush *et al.,* 2016; Ullah *et al.,* 2022).

Q FEVER AS A NEGLECTED ZOONOSIS IN NIGERIA

In Nigeria, Q fever remains a neglected zoonotic disease because its public health significance is still largely unknown. Data on its prevalence and mortality rate especially in humans is limited and it is also not a reportable disease in Nigeria. To a large extent, the studies that have been carried out on this disease have been mostly in animals and only recently in humans with the first report believed to be by Addo and Schnurenberger (1977). The distribution of the disease in Nigeria is reportedly common in the North-west, North-east, South-west regions, sparse in North-central and none reported in the South-east and South-south of the country (Baba *et al.,* 2023). Also, almost all of these studies conducted to date have used serological techniques with the most recent being ELISA.

Further studies to better understand the bacterium and its pathogenesis in humans especially with the use of molecular genetic techniques is essential as they can define more precisely the incidence, clinical spectrum, treatment, morbidity and mortality associated with Q fever in humans (Porter *et al.,* 2011).

Further research on the development and use of recombinant vaccines for prevention of infection at a herd level but also in human populations as well as animal vaccination and vaccination of individuals at high risk of exposure or/and of severe clinical disease would significantly reduce the zoonotic risk. Constitution of awareness programs and their implementation on the public health significance of this disease are of utmost importance in Nigeria because Q fever is largely unknown to those occupationally at risk such as pastoralists, abattoir workers and livestock owners. To succesfully combat this disease, it is essential to prioritize this disease under a “One health” concept.

CONCLUSION

Q fever remains a neglected disease in many developing countries including Nigeria. *Coxiella burnetii* is a hardy pathogen that can be sustained in harsh environmental conditions. Q fever is mostly asymptomatic in animals and thus poses a high risk of infection in humans. Pathobiological studies to enable better understanding of the bacterium and its pathogenesis in humans especially with the use of molecular genetic techniques are essential for Q fever management. In addition, awareness programs on the public health significance of this disease in humans especially for those at risk would be helpful in its prevention and control.

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