REVISTA DO INSTITUTO DE MEDICINA TROPICAL DE SÃO PAULO

JOURNAL OF THE SÃO PAULO INSTITUTE OF TROPICAL MEDICINE

REVIEW

http://doi.org/10.1590/S1678-9946202365039

Overview of Q fever in Brazil: an underestimated zoonosis

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ABSTRACT

This review aims to provide current information about Q fever, elucidating the etiological, epidemiological, pathogenic, clinical, diagnostic, therapeutic, and prophylactic aspects of the disease for the medical community. We discuss the main forms of presentation of the agent, its ability to persist in the body, the infinite possibilities of susceptible hosts, the main known forms of transmission, its importance in populations at occupational risk, and the role of arthropods in the natural history of the disease. Focusing on Brazil, we present the cases already described and studies developed since its first report, and how there is still much to unravel. We are aware of the possibilities of the persistence of the agent and the development of severe clinical pictures and the specific treatments currently instituted. We also wish to raise awareness about the future, the new genotypes that are emerging, the need to study the effects of vaccines, and the impact of Q fever on the population. Q fever is a poorly understood disease in Latin America, and recent studies, especially in Brazil, have revealed the importance of developing new studies.

KEYWORDS: Q fever. *Coxiella burnetii.* Zoonosis. Emerging diseases.

INTRODUCTION

Q fever is a human disease caused by the bacterium *Coxiella burnetii*. This pathogen can infect vertebrate and invertebrate animals and cause a disease termed coxiellosis[1]. The use of a different nomenclature for the disease in animals and humans is due to the difference in the most common clinical presentation, with reproductive disorders being the most common clinical presentation in animals and a febrile disease with nonspecific symptoms in humans[1].

Increased knowledge about the disease in recent decades has led to the identification of outbreaks worldwide, suggesting that the bacterium is dispersed across all continents[2,3]. Since the first serological evidence of *C. burnetii* presence in Brazil by Brandao *et al*.[4] in the 1950s, few studies have been published in the country, keeping the disease in the shadows.

C. burnetii is a highly transmissible zoonotic agent that infects a wide range of animal species through different routes of transmission[5]. As in Australia, Q fever is widely studied in various European countries, and several outbreaks in animals and humans have been documented[2]. In Brazil, the disease is still widely underestimated, not well known by doctors and veterinarians, and depends on more clinical and epidemiological studies to raise awareness of the situation within the country and to enable efficient control and preventive measures[6].

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Received: 16 January 2023

Accepted: 25 April 2023

Etiology

C. burnetii is a gram-negative, pleomorphic, and obligate intracellular bacterium[1]. Due to its ability to enter cells and replicate, it was taxonomically classified in past decades within the Rickettsiae group due to the impossibility of its isolation in an axenic medium and its ability to infect arthropods. Although there are some similarities with Rickettsiae, current knowledge confirms that *C. burnetii* does not belong to the group, mainly due to its placement in phylogenetic inferences using sequences of the 16S rRNA gene where *Coxiella* showed a close relationship to the order Legionallales, distancing it from the Rickettsiales[1]. In addition, several factors, including metabolism, infectivity, morphological variations during infection, and the ability to form spores, also support the reclassification into the Coxiellaceae family[7].

Inside infected cells, *C. burnetii* can present as a large-cell variant (LCV), which is metabolically active, and as a small-cell variant (SCV), which is a spore-like structure that confers extracellular survival and high environmental resistance[8]. SCVs differentiate from LCVs only in the intracellular environment after infecting the host, becoming metabolically active and virulent during the stationary phase of the *C. burnetii* growth cycle, involving changes to the cell surface of the bacteria[9]. Due to stress resistance, when excreted by the host organism, SCV can remain for months in the environment, soil, and animal products, even at high temperatures[10,11].

The LPS of *C. burnetii* is a critical virulence factor of the bacterium, a structurally and antigenically distinct protein present in different types[12]. There is a configuration of LPS named Phase I LPS, which is related to the complete epitope with the presence of the O-chain; this structure is observed in wild-type *C. burnetii* and confers virulence[12]. There is another configuration of LPS, named Phase II LPS, which is only observed after several passages in the laboratory using cell culture and is characterized as the result of the loss of the O chain of Phase I LPS, related to the deletion of a gene during laboratory manipulation[12]. *C. burnetii* expressing Phase II antigens are avirulent and cannot be found in nature. There are other intermediate forms of LPS, but for diagnosis and treatment purposes, these two configurations are more important[13].

The LPS layer of *C. burnetii* has a different relationship with the immune system. In primo-infection, patients presenting acute Q fever initially elicit an Anti-Phase II immune response[14]. The rise of Anti-Phase II antibodies can be observed between 7 to 15 days after the onset of the disease[15]. With the infection progression, Anti-Phase I antibodies increase and can become prevalent in the serum, with Anti-Phase II antibodies declining between 3 and 6 months post-infection[14]. The acute immune response of Q fever is initially related to the presence of Anti-Phase II antibodies, whereas persistent Q fever is linked to high titers of Anti-Phase I antibodies[12,15]. These data are important for a better understanding of Q fever prevalence studies and can be best checked in Table 1.

An infectious dose of < 10 *C. burnetii* cells inoculated via the respiratory route is sufficient to generate the disease and for that reason it is placed in category B by the Centers for Disease Control and Prevention (CDC) as a potential risk to human health and the second highest priority for countering bioterrorism[13].

Epidemiology

In Brazil, although Q fever was introduced as a compulsory notification disease in 2014 (Ordinance 1.271 of June 6, 2014, of the Ministry of Health), the reported cases are counted with other Rickettsioses, which does not allow us to count the actual cases of Q fever, generating confusion about its status as a compulsory notification disease.

In most serological surveys conducted since 1953, people and animals sensitized by the bacterial species were studied, confirming its circulation in some states of the country, such as Rio de Janeiro, Sao Paulo, Minas Gerais, Ceara, Alagoas, Goias, Rio Grande do Sul, Mato Grosso do Sul, Pernambuco, Santa Catarina and Piaui[16-26]. Q fever has an occupational character, with many of its articles demonstrating the occurrence of this disease in butchers, veterinarians, farmers, and other professionals who have contact with farm animals[4,13,20,27-31].

Table 1 - Relationship antibodies produced against both antigenic phases of *C. burnetii* and the confirmation of Q fever cases.

Disease evolution	Anti-Phase II antibodies	Anti-Phase I antibodies
Acute Q fever (weeks after infection)	Peak between 7 and 15 days post-infection (+IgM, -IgG); Stability after 2 to 3 weeks (+IgM, +IgG)	Low amount at symptom onset (undetectable); Start of antibody production (+IgM, -IgG)
Persistent Q fever (months and years after infection)	Constant decrease after 6 months (-IgM, +IgG)	Prevalence after six months of infection (-IgM, +IgG)

Source: Anderson *et al.*[13].

C. burnetii is an opportunistic bacterium that can infect many animal species, such as cattle, sheep, goats, dogs, cats, birds, small rodents, and arthropods[1]. Although *C. burnetii* infects a variety of animals, small ruminants are known to be the major disposers of the bacteria in the environment through abortions and parturition and are thus the main hosts of the agent[13]. Goats and sheep are responsible for disease outbreaks, setting them alongside cattle as the primary sources of infection for humans and the animal species of greatest importance in the chain of transmission of Q fever[32].

Airborne route: infected mammalian females are very important for the chain of transmission because the microorganism has tropism for the placenta, and at the time of delivery, there is aerosolization, which often results in outbreaks on the property[32]. The bacterium is capable of traveling up to 30 km with the wind through aerosolization[11]. This is the main transmission route of *C. burnetii* and may be one of the hypotheses for the occurrence of Q fever cases in urban populations with no history of travel to rural areas, who do not consume raw milk or have no contact with infected animals, abortion remains or fecal material (which would be the other possible transmission routes)[18].

Arthropods: arthropods are of little epidemiological importance to humans, as they have a small potential of transmitting the bacteria[1]. Transmission to humans would only be possible with very young, small ticks that are practically imperceptible to the human eye and are and can attach to the surface of an individual for a prolonged period[32]. However, they are relevant amplifiers of bacteria for animal infection due to factors such as attack rate, host preference and contact time[33]. In Brazil, *Amblyomma cajennense*, *Rhipicephalus sanguineus* and *Dermacentor nitens* are the most important, present in all regions of Brazil, both in rural and urban areas, and can affect ruminants and companion animals[1,33].

Ruminants: contact with ruminants is a significant risk factor associated with *C. burnetii* infections, especially close to birth or during miscarriage, when a large amount of bacteria is released into the environment and the possibility of infective aerosol generation is increased, which may affect the rural workers, residents, and other animals that come into contact with placental remains[11]. Moreover, the spore-like forms from infected animals are released into the environment and persist in wool, feeders, water troughs, stables, utensils, equipment, pasture, and feces, resulting in the biological contamination of the environment with significant risk to human health[34].

Products of animal origin: due to the tropism of the bacteria by the mammary gland, the consumption of raw unpasteurized milk and its derivatives, which is common in Brazil, appears to be a possible transmission route of the agent[35].

Wild animals: except for people who are used to ecotourism or populations that live in forest areas, such as indigenous populations, *C. burnetii* infection does not present a risk to humans[32]. Nevertheless, one should consider the epidemiological possibilities with the advent of today's environmental conflicts and the importance of wild animals in keeping the agents in circulation and serving as a source of infection for farm animals[32]. Furthermore, depending on the epidemiological scenario, wild animals can serve as reservoirs for human disease and represent a public health risk. In Brazil, *C. burnetii* has been detected in bats, rodents and cervids[17,25].

Person-to-person transmission: although rare, cases have been reported in hospital-acquired infections, congenital infections, blood transfusions, sexual intercourse, and contact with an infected woman in labor[36,37].

Brazil's current situation

There is a lack of information regarding the disease's epidemiology in Brazil, with only a few focal prevalence studies and case reports that do not represent the actual situation in the country[18].

Animal models

A study conducted in 2018, in Sao Paulo State, identified a prevalence of 23.8% of infected bovine slaughterhouse animals[16]. The samples were tested by indirect immunofluorescence (IFA), and those that reached titers equal to or greater than 64 were considered positive. The antigen used for the technique was from an Argentinean At12 strain isolated from *Amblyomma tigrinum*. This work highlights the risk to public and animal health due to the possibility of dissemination of the agent in the environment that can lead to outbreaks of abortions in production animals and human illness among producers and rural workers, as well as for final consumers of animal products[16]. In addition, the same authors obtained genotyping results that point to the presence of diverse strains already reported in the world literature, further highlighting the need for molecular epidemiology studies and virulence studies of the national strains[24]. The report of a unique genotype in Argentina further highlights the presence of regional strains of the bacterium in Latin America[24].

A study conducted in 2018, in Pernambuco State, found seroprevalences of 2.1% and 2.2% in goats and sheep, respectively. The prevalence of this study was determined by indirect immunofluorescence (IFA) using the same At12

strain described above and considering the animals with titers equal to or greater than 64 as positive[31]. By molecular methods, *C. burnetii* was found in raw milk and artisan cheeses commercialized in Goias State and Minas Gerais State, highlighting the public health risk of consuming dairy products[23,38].

In addition to ruminants, studies have indicated the possibility of the disease occurring in wild reservoirs. In 2016, the etiologic agent was detected among military firefighters of Ribeirao das Lajes city, Rio de Janeiro State, who had contact with goats and capybaras[20]. In 2018, the same group confirmed the presence of *C. burnetii* in bats and wild rodents in Brazil's Southern states, demonstrating the variety of reservoir possibilities and the need for epidemiological surveys to better characterize the primary reservoirs for human diseases and subsequent implementation of control measures[17,25].

Human models

Prevalence studies of human Q fever in Brazil have only been conducted in the Southeastern states, with prevalence ranging from 1.63% to 62.5%, and high rates observed in occupational groups such as slaughterhouse workers and veterinary students. In Sao Paulo city, two surveys from the 1950s investigated *C. burnetii* in asymptomatic dairy farm workers on dairy farms and slaughterhouse workers, revealing positivity rates of 7% and 1.63%, respectively, using the complement fixation test as the serological method[4,31].

Over time, other studies with small sample sizes and diagnostic techniques still under evaluation were performed, such as a study carried out in the Vale do Paraiba region with dairy farm workers and another one carried out in Belo Horizonte city with slaughterhouse workers whose main focus was the study of toxoplasmosis, which showed, for the first time, a high prevalence among the human population tested in the country[28,29].

Over the years, and with the improvement of serological diagnosis techniques, between 2005 and 2009, a group of researchers from Juiz de Fora city and Sao Paulo city investigated the occurrence of Q fever among healthy and unhealthy individuals, with the highest seropositivity ever found of 62.5% in febrile patients with signs of pneumonia attended in health care units in Minas Gerais State, and the first diagnosis of endocarditis by *C. burnetii* was described[39-41]. In 2008, *C. burnetii* endocarditis was described for the second time in Brazil, this time in Sao Felipe municipality, Bahia State, being the only case of the disease described in the state[42]. Additionally, in 2009, a study group from Rio de Janeiro city conducted an important and unprecedented prevalence study in the HIV-positive population in the country, starting a series of investigations in the state[43].

In recent years, some studies have been conducted with symptomatic populations. These populations had clinical signs of dengue, and without laboratory test confirmation, they were diagnosed with Q fever. Mares-Guia *et al.*[21] confirmed the presence of 10% seropositive individuals in Itaborai municipality, Rio de Janeiro State. Meurer *et al.*[22] confirmed the presence of 5.3% seropositivity in Minas Gerais State. França *et al.*[18] confirmed the presence of 21.4% seropositive patients in Sao Paulo State. These studies corroborate the need for more studies in the Southeastern region and at a national level and the possibility of Q fever as a differential diagnosis for dengue. The study carried out in Sao Paulo State, the most populous state in the country, evaluated a very expressive sample of febrile patients and made it possible to analyze not only the prevalence of the disease, but also the profile of these positive-testing patients concerning age, duration of symptoms, place of residence, antibody titers and gender[18].

In addition to the serological investigations, a study from 2015 revealed the agent's presence by molecular methods in heart valves from endocardial patients with negative cultures[44]. These data point to the importance of Q fever in persistent infection episodes and the possibility of cardiac patients without a proper diagnosis in the national territory[44]. This study, and others, can be seen in Table 2, as well as some of their details.

Due to the asymptomatic character at the onset of infection and symptoms similar to those of common influenza, it is estimated that the prevalence is much higher in Brazil, a tropical and developing country with several wild and farm animal species that act as reservoirs for *C. burnetii*[18]. Q fever is underdiagnosed and not well known among doctors and veterinarians, with a small number of centers for laboratory diagnosis and few studies concerning the identification and characterization of *C. burnetii* in humans, animals and the environment[18]. To date, 15 studies have reported direct or indirect evidence of Q fever cases in humans (Figure 1).

Pathogeny

As Toman *et al.*[12] described, *C. burnetii* has particular mechanisms that give it versatility and the ability to survive and replicate in different hosts. These mechanisms are modulated by effector proteins released by a type IVB secretion system with unique functions and features to evade the immune system[12]. Among these mechanisms, we can highlight:

Table 2 - Studies of Q fever in humans conducted in Brazil.

Publication year	Publication subject	Diagnostic test	Antigen	Positivity definition or cut-off	Study location	Positivity	Article
1953	Serological study of workers in a meat processing plant	Complement fixation test	Nine Mile	Titers 1:1	Sao Paulo city, Sao Paulo State	1.69%	Brandao *et al*.[4]
1954	Q fever in Rio de Janeiro.	Complement fixation test	Nine Mile	Titers 1:4	Rio de Janeiro city, Rio de Janeiro State	1.8%	Travassos *et al*.[30]
1955	Q fever research in Sao Paulo: a study of cattle handlers	Complement fixation test	Nine Mile	Titers 1:8	Sao Paulo city, Sao Paulo State	7%	Valle[31]
1964	Prevalence among milkers and dairy cattle workers	Capillary serum agglutination	Nine Mile	Titers 1:4	Vale do Paraiba, Sao Paulo State	8.5%	Ribeiro-Netto *et al*.[28]
1975	*Toxoplasma gondii* and *Coxiella burnetii* among Brazilian slaughterhouse workers	Microagglutination	Nine Mile	Titers 1:4	Belo Horizonte city, Minas Gerais State	29%	Riemann[29]
2005	Serological evidence in healthy individuals from the Juiz de Fora, Minas Gerais State	Indirect immunofluorescence assay	Nine Mile	Titers 1:16	Juiz de Fora city, Minas Gerais State	3.9%	Costa *et al*.[39]
2006	Report of 16 cases of Q fever in Minas Gerais	Indirect immunofluorescence assay	Nine Mile	Titers 1:32	Juiz de Fora city, Minas Gerais State	62.5%	Costa *et al*.[40]
2006	Infective endocarditis, experience in a cardiology hospital in Sao Paulo	Indirect immunofluorescence assay	Nine Mile	Titers 1:800	Sao Paulo city, Sao Paulo State	1.63%	Siciliano *et al*.[41]
2008	*Coxiella burnetii* endocarditis: case report	Indirect immunofluorescence assay	Nine Mile	Titers 1:1600	Sao Felipe city, Bahia State	Positive case	Siciliano *et al.*[42]
2009	*Coxiella burnetii* seroprevalence in HIV-positive patients in Jacarepagua, Rio de Janeiro State	Indirect immunofluorescence assay	Nine Mile	Titers 1:64	Rio de Janeiro city, Rio de Janeiro State	3.2%	Lamas *et al*.[43]
2015	*Bartonella* spp. and *Coxiella burnetii* associated with culture-negative endocarditis	Indirect immunofluorescence assay	Nine Mile	Titers 1:800	Sao Paulo city, Sao Paulo State	7.8%	Siciliano *et al*.[44]
2016	Dengue suspected patients in Itaborai, Rio de Janeiro State	Indirect immunofluorescence assay	Nine Mile	Titers 1:64	Itaborai city, Rio de Janeiro State	10%	Mares-Guia *et al.*[21]
2018	Military service firefighters, Rio de Janeiro, Rio de Janeiro State	Indirect immunofluorescence assay	Nine Mile	Titers 1:64	Rio de Janeiro city, Rio de Janeiro State	5 cases	Lemos *et al.*[20]
2020	Dengue suspected patients in Minas Gerais	Indirect immunofluorescence assay	Nine Mile	Titers 1:64	Minas Gerais State	5.72%	Meurer *et al*.[22]
2022	Dengue suspected patients in Sao Paulo	Indirect immunofluorescence assay	At12 and Nine Mile	Titers 1:64	Sao Paulo State	22.5%	França *et al*.[18]

Source: Adapted from Mares-Guia *et al*.[21].

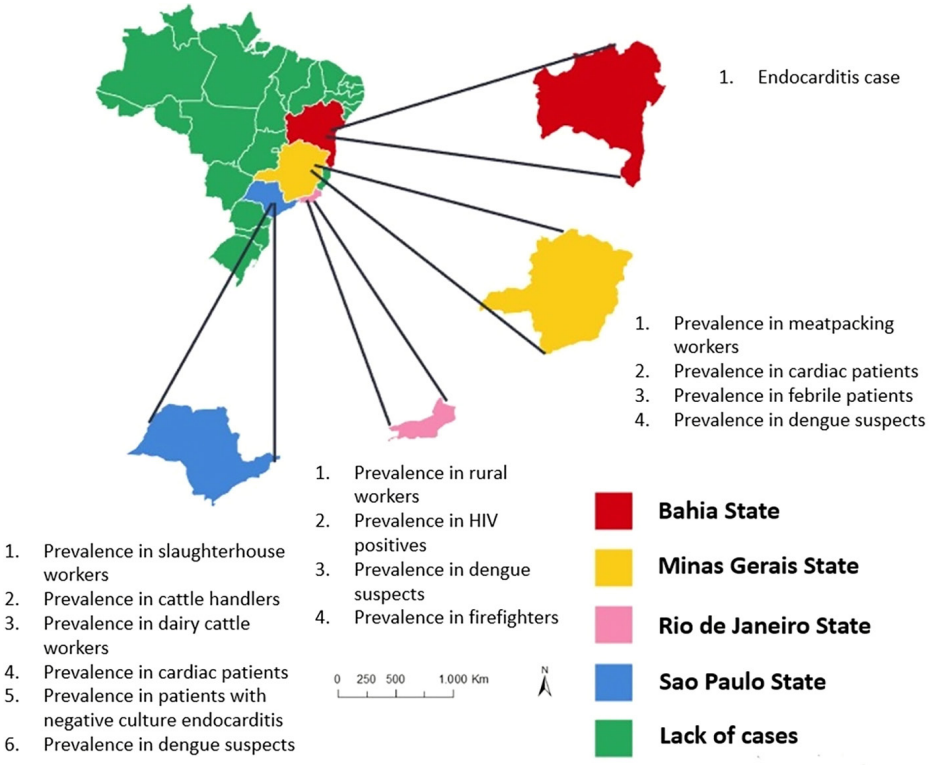

Figure 1 - Brazilian states with reports and studies of Q fever.

- Action against the activation of reactive oxygen intermediates (ROI) and reactive nitrogen intermediates (RNI), the main mechanisms of innate immunity capable of fighting intracellular *C. burnetii*;
- Growth restricted to a low oxygen environment;
- Release of cations and DNA repair enzymes, allowing the genome to be as small as possible to survive in the environment;
- Bacterial LPS can antagonize TLR4 receptors and limit immune activity in several ways, including penetrating cells through the interaction between the O-chain and lipid rafts;
- Manipulation of signaling mechanisms of infected host cell, preventing its action against *C. burnetii*;
- Use of cellular kinases and cytoplasmic lipids for the biogenesis of the parasitophorous vacuole (PV) for replication. *C. burnetii* resists the degradative functions of the vacuole and exploits the acidic pH for metabolic activities;
- Anti-apoptosis activity with the secretion of Bcl-2 protein;
- Autophagic cell recycling activity by the secretion of the Beclin-1 protein;
- Tropism by adipose and placental tissues, strategic for escaping immune surveillance and establishing replicative activity.

It is suggested that inhaled bacteria tend to generate pulmonary complications, while ingestion of contaminated raw milk tends to generate hepatopathies; however, this may also be related to the strain involved[9]. The acute disease occurs as a consequence of the genotype involved, while the bacterial persistence is linked to predisposing factors of the individual[9].

Clinical signs

C. burnetii is a highly infectious bacterium, and its virulence will depend on the genetic variant[9]. In 60% of cases, it is usually asymptomatic in humans, which makes it difficult to control the disease, removing with time the epidemiological link for association[45].

Acute Q fever

Regarding symptoms, acute cases occur more frequently (35% to 39%), especially in situations of immunosuppression, although immunocompetent patients may express clinical signs of the disease[46]. The acute disease, in most cases, is similar to common cold, accompanied by fever, headache, myalgia and a cough, with some cases developing into pneumonia and hepatitis[46]. Complications during the acute phase can occur, with massive replication of *C. burnetii* in specific regions of the body and the development of atypical

pneumonia, arthralgia, muscle lesions, encephalitis, lymphadenomegaly, hepatomegaly and splenomegaly[47].

Persistent Q fever

Innate immunity is extremely limited for combating Q fever, and the outcome of the infection depends on cellular immunity and its efficiency in stopping *C. burnetii* replication[12]. Persistent infections, therefore, are more frequent in immunocompromised patients, pregnant women, or patients with preexisting diseases in the target organs of the bacteria, such as heart valve disease patients[48]. Persistent infections are less frequent (1% to 5%) but can be detected for months to years. It is possible to notice this with the emergence of studies and reports involving endocarditis patients with anti-*C. burnetii* antibodies and negative cultures for other common bacteria[11].

Endocarditis is the main chronic condition evident in patients who develop persistent Q fever[11]. One patient in every hundred usually develops endocarditis 6 to 18 months after infection. The most affected group is people over 50 years of age[11,44]. Most of these patients already have a previous valvular disease, and this is therefore a factor that should always be considered when treating a patient suspected of having Q fever[11]. It is worth emphasizing the importance of serologic follow-up of infected patients every 3 to 6 months, considering that endocarditis has been documented in infected patients for 20 years[44]. Echocardiography is used for the diagnosis of infective endocarditis and is associated with high titers of Phase I antibodies (equal to or greater than 800), suggesting that its cause is *C. burnetii*[1]. Confirmation is only possible from the patient's valve PCR after surgical procedure or death[11]. Although there is no confirmation in the diagnostic routine, treatment should be instituted in the same way[11].

Diagnosis

Diagnosis is based on established clinical-epidemiological and laboratory criteria. Laboratory diagnosis involves direct and indirect methods, depending on the sample type, the period in which it was collected, and the species of origin.

Direct diagnostic methods

Microbiological diagnosis:

- *Bacterial isolation in cell culture*: The material of choice for isolation will also depend on the clinical presentation of the patient; however, blood, plasma, cerebrospinal fluid, bone marrow, heart valves, aneurysms, vascular prostheses, liver biopsies, and placenta are usually suitable materials[12]. Embryonic lung fibroblasts are most often used for culture because they are more susceptible to infection[12]. Isolation of *C. burnetii* should only be performed in a biosafety level 3 laboratory because of its extreme infectivity[12].
- *Bacterial isolation by axenic media (ACCM2)*: The material of choice will depend on the patient's clinical presentation, and this is a recent method under evaluation[49]. It is a semisolid medium that supports robust growth of *C. burnetii* via colony formation on agarose plates[49]. It has the advantage of overcoming the need for purification required for further molecular analysis of isolates and reducing animal use for isolating the bacteria[12]. However, it has been reported that some genotypes (ST1–7/30, ST8, and ST9–10/27–28/30 groups) do not grow in this medium. All these strains have a QpRS plasmid. Hence, its use for primo isolation from clinical samples may not be indicated[49].

Molecular diagnosis: the primary technique used by specialized laboratories, both for the acute and persistent phases, is real-time polymerase chain reaction (qPCR), where the target of the reaction is usually the *IS1111* gene due to its high diagnostic sensitivity[23]. This method allows detection of the agent from serum, blood, cerebrospinal fluid, tissue and milk samples[12]. Molecular diagnosis is the most sensitive method for detecting recent infections when serology cannot be used due to the absence of antibodies. However, after 17 days of infection, the DNA of *C. burnetii* becomes undetectable by the technique because as antibodies are produced, the bacteria stop circulating, limiting molecular diagnosis[12].

Indirect diagnostic methods

- Serological diagnosis: laboratory confirmation of acute Q fever is defined by the presence of Anti-Phase II antibodies approximately 7 to 21 days post-infection when seroconversion occurs with IgG titers equal to or greater than 200 and IgM titers equal to or greater than 50[32]. Persistent Q fever (formerly known as chronic Q fever) is defined by the presence of Anti-Phase I antibodies with IgG titers equal to or greater than 800, and when lower, this titer is considered the result of residual antibodies and not of a properly active infection[32] (Table 1).
- Indirect Immunofluorescence Reaction (RIFI): the gold standard for diagnosing the disease in humans. Phase I and II strains of *C. burnetii* are used to perform the technique. The technique presents superior sensitivity and specificity compared to ELISA for IgM and IgG[13].

Paired sample collections are preferred, with 2 to 3 weeks between collections, to establish a more effective diagnosis by comparing the increase of titers over a period of time. In summary, it is the method of choice for the clinical monitoring of infected patients[13].

- Indirect Enzyme Immunoassay (i-ELISA): the gold standard for diagnosing the disease in animals has also been widely used to diagnose the disease in humans[13]. Some commercial kits detect the different immunoglobulins produced against Phase I and Phase II[13].

The serological method is the method of choice for analyzing human samples because it is sensitive, specific, inexpensive, fast, safe, and easy to perform[32]. However, cross-reactions can occur with species of the genera *Bartonella* and *Legionella*, especially in persistent infections with the differential diagnosis of endocarditis and pneumonia[13]. qPCR is essential for the early diagnosis of acute Q fever in serum samples, considering that when immune defenses are built up, the bacteria become undetectable. In Brazil, qPCR and RIFI are the methods used by national surveillance laboratories[13,34].

Treatment

Acute Q fever

Although most acute infections resolve spontaneously, antibiotic therapy significantly reduces the duration of symptomatic illness and the likelihood of persistent infection and should therefore be performed[32]. Antibiotic therapy for Q fever treatment usually takes approximately 14 days, and patients should be monitored by laboratory tests to evaluate their recovery[32]. The recommended drug for acute cases is doxycycline, 100 mg daily. The efficacy of other antimicrobials is still uncertain and requires further study[13].

Persistent Q fever

The treatment for persistent Q fever requires a higher pharmacological dosage and a longer treatment regimen of doxycycline and hydroxychloroquine for 18 months[32]. In this case, the association with hydroxychloroquine is essential because it can alkalinize *C. burnetii* VP and potentiate doxycycline's activity[32]. Although there is this indication, and studies show trials for this application, a recently published study does not recommend the use of hydroxychloroquine for the treatment of Q fever, stating that this is not an evidence-based clinical recommendation[50]. To date, there are no published randomized trials evaluating the best protocol, and no ongoing trials are currently registered[50].

In persistent infections, specific cases of focal lesions are observed, and the treatment should be better directed to address these situations[47]. Patients with endocarditis, for example, require surgical intervention as an adjunct[47]. Acknowledging the time it takes for seroconversion and the difficulty of a complementary diagnosis in the health care system, treatment should be instituted as soon as Q fever suspicion is assumed, and laboratory monitoring should be performed to confirm it[13]. In contrast, persistent infections should not be treated without a definite diagnosis due to the complexity of the therapy[13].

Specific treatments

Children and those allergic to doxycycline: rifampicin and cotrimoxazole are alternatives for those under eight years old or allergic to doxycycline[32].

Endocarditis: the treatment of acute infection is very important to prevent the development of endovascular disease, even in patients with previous cardiac disease[11]. As mentioned previously, there is a discussion about the association of hydroxychloroquine and doxycycline for the treatment of persistent Q fever, however, only treating with doxycycline, 200 mg daily, depending on the specificity of the patient, is currently the safest alternative for this condition[11]. Associated with antibiotic therapy, the surgical procedure directed to the affected valves is necessary[47].

Nervous system infection: due to their ability to cross the blood-brain barrier, fluoroquinolones are recommended for patients with neurological signs[32].

Pregnant women: pregnant women should undergo combination therapy with trimethoprim and sulfamethoxazole as soon as possible[32]. In addition, a study confirmed that prolonged treatment of these women for more than five months could prevent complications during pregnancy[32].

Prevention and control

There is a vaccine tested and licensed to protect workers at occupational risk in Australia, although there are still adverse reactions and an improvement project has been proposed[51]. However, in Brazil and the rest of the world, vaccinating humans has not yet been approved and requires further studies regarding its impact on these workers and a measure by national health agencies[52].

The control of the disease in humans is directly linked to the control of the disease in animals; therefore, the health evaluation and diagnosis of livestock through the surveillance of abortions, animal transit under intense sanitary control, and combating the consumption of uninspected food of animal origin are the main strategies

to prevent and control the transmission of the disease[13]. Furthermore, for those at occupational risk, it is essential to use personal protective equipment when handling animals, especially abortion and birth products, take proper care to sanitize the animal facilities, and vaccination, which is not available in Brazil, before primary infection, which, although it does not protect against infection itself, can reduce the excretion of *C. burnetii*[6].

Q fever surveillance covers the concept of One Health[18]. It involves the protection of the general population, investigating and mapping the incidence of the disease, always associating outbreaks in animals with the possibility of outbreaks in humans, and identifying the possible environmental source of infection due to high environmental resistance[18].

CONCLUSION

The need to consider Q fever as an important airborne and foodborne disease in Brazil can ensure greater safety of milk and meat handling in dairy farms and slaughterhouses nationwide and expand surveillance of disease outbreaks on farms in affected states. Furthermore, with the recent findings of high prevalence in farm animals and humans, the zoonotic potential of *C. burnetii* needs to be considered, especially for those implementing measures to prevent and control Q fever outbreaks. Clinical and molecular studies involving the occurrence of Q fever in human patients with pneumonia (acute disease) and endocarditis (persistent disease) are needed to discover the impact that this infection has on populations in Brazil beyond fever and animal abortions. We strongly recommend the development of clinical studies in Brazil to observe how patients respond to the different proposed treatments and the real efficiency of hydroxychloroquine for the treatment of endocarditis. Comprehensive studies are also needed from the One Health perspective, verifying the presence of the bacteria in farm animals, people in contact with these animals, and the environment in which both are located, to have a greater perspective on the epidemiology of this disease and how it truly affects populations.

AUTHORS' CONTRIBUTIONS

DAF: conceptualization, data curation, formal analysis, investigation, methodology, validation, visualization, writing (original draft), writing (review and editing); MSRM, JF, ERSL, AILD, MVFS, HL: supervision, validation, visualization, writing (review and editing); JM: conceptualization, funding acquisition, project administration, resources, supervision.

FUNDING

DAF received financial support from National Council for Scientific and Technological Development (CNPq), grant Nº 155904/2019-1.

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