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LITERATURE REVIEW

Approach of the epidemiological situation of *Coxiella burnetii* in South America: A systematic review

Abordaje de la situación epidemiológica de Coxiella burnetii en América del Sur: Una revisión sistemática

Abordagem da situação epidemiológica de Coxiella burnetii na América do Sul: Uma revisão sistemática

Andrea K Alvarez-Osorio[1]; Miguel H Parra[2]; Carolina Montoya-Ruíz[3*]

[1]*Departamento de Ciencias Biológicas, Universidad de los Andes, Cra. 1 #18a-12, Bogotá, Colombia.*
[2]*Gibat and Inmubo Group. Facultad de Medicina. Universidad el Bosque, Ak. 9 #131a-2 Bogotá, Colombia.*
[3]*CRS-TID center for research and surveillance of tropical and infectious diseases- Grupo Biotecnología animal. Facultad de Ciencias, Universidad Nacional de Colombia - Medellín, Cra. 65 #59a-110. Colombia.*

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***Corresponding author:** Facultad de Ciencias, Universidad Nacional de Colombia, Medellín, Colombia CRS-TID center for research and surveillance of tropical and infectious diseases- Grupo Biotecnología animal cmontoyru@unal.edu.co; carolinamontoyaruiz@gmail.com

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Abstract

Background*: Coxiella burnetii* is recognized as the causative agent of Q fever, a zoonotic disease affecting both humans and animals. It exhibits antigenic variation in two phases: Phase I and Phase II. The latter is primarily linked to the acute form of Q fever, characterized by symptoms such as pneumonia and hepatitis. This acute manifestation can affect various mammal species includes humans. **Objective**: Due to the limited information available in South America, we conducted a systematic review of its epidemiology between 2000 and 2024 to consolidate data. This review was complemented by an assessment of the presence of IgG Phase II antibodies in a population of 177 people in the province of Córdoba, Colombia. **Results:** Epidemiological data revealed the presence of this pathogen in humans, animals, and even food sources, with variable seropositivity rates varying by region for both humans and animals. Notably, most registered cases in humans were associated with the acute phase, while most animals displayed reproductive issues. The evaluation of IgG Phase II antibodies in the population of Córdoba, indicated a seropositivity rate of 4.52%. **Conclusion:** These findings underscore the reality that *C. burnetii* poses a significant and possibly underestimated threat in Latino America and Colombia.

Keywords: *antibody detection; Coxiella burnetii; epidemiology; Q fever; risk factors; South America.*

Resumen

Antecedentes: *Coxiella burnetii* es el agente causal de la fiebre Q, enfermedad zoonótica que afecta tanto a humanos como a animales. *C. burnetii* presenta variación antigénica en dos fases: Fase I y Fase II. Esta última está relacionada principalmente con la forma aguda de la fiebre Q, caracterizada por síntomas como la neumonía y la hepatitis, que puede afectar a varias especies de mamíferos, incluido el ser humano. **Objetivo:** Con el fin de consolidar

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la información de este patógeno en Suramérica, se realizó una revisión sistemática de artículos publicados sobre *C. burnetii* entre los años 2000 y 2024. Esta revisión se acompañó de una evaluación de la presencia de anticuerpos IgG Fase II en una población de 117 personas en Córdoba, Colombia. **Resultados:** Los estudios epidemiológicos demostraron la presencia de *C. burnetii* en humanos, animales e incluso alimentos con diferentes valores de seropositividad según la región. Los estudios en humanos registraron principalmente asociaciones con la fase aguda, mientras que los estudios en animales evidenciaron manifestaciones asociadas principalmente a problemas reproductivos. La evaluación de anticuerpos IgG de fase II en la población de Córdoba registró una seropositividad del 4,52%. **Conclusión:** Estos resultados muestran la presencia y amenaza significativa subestimada de *C. burnetti* en Lationámerica y Colombia.

Palabras clave: *Coxiella burnetii; epidemiología; evaluación anticuerpos; factores de riesgo; fiebre Q; Suramérica.*

Resumo

Antecedentes: A *Coxiella burnetii* é o agente causador da febre Q, uma doença zoonótica que afecta tanto o homem como os animais, com variação antigénica em duas fases: Fase I e Fase II. Esta última está principalmente relacionada com a forma aguda da febre Q, caracterizada por sintomas como pneumonia e hepatite, que pode afetar várias espécies de mamíferos, incluindo o homem. **Objetivo:** Para consolidar a informação sobre este agente patogénico na América do Sul, foi realizada uma revisão sistemática de artigos publicados sobre *C. burnetii* entre 2000 e 2024. Esta revisão foi acompanhada por uma avaliação da presença de anticorpos IgG Fase II numa população de 117 pessoas em Córdoba, Colômbia**.** **Resultados:** Estudos epidemiológicos demonstraram a presença de *C. burnetii* em seres humanos, animais e até mesmo em alimentos, com valores de seropositividade diferentes consoante a região. Os estudos em humanos registaram principalmente associações com a fase aguda, enquanto os estudos em animais mostraram manifestações associadas principalmente a problemas reprodutivos. A avaliação de anticorpos IgG de fase II na população de Córdoba registou uma seropositividade de 4,52%. **Conclusão:** Estes resultados

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mostram a presença e a ameaça significativa e subestimada de C. burnetti na América Latina e na Colômbia.

Palavras-chave: *América do Sul; avaliação de anticorpos; Coxiella burnetii; epidemiologia; fatores de risco; febre Q.*

Introduction

Coxiella burnetii is an intracellular, gram-negative, spore-producing bacterium that is characterized as the etiological agent of Q fever This microbiological agent is characterized by being a small gram-negative bacillus (0.30-1.00 µm) (Eraso-Cadena *et al.,* 2018). This bacterium is characterized by its transmission mainly as a zoonotic agent associated with inhalation processes and contact with biological substances such as urine, feces, milk and placental products of infected animals (Eraso-Cadena *et al.,* 2018). Another relevant characteristic of this microorganism is the fact that it presents antigenic variation (da Costa *et al.,* 2006).

In Phase I, the bacterium synthesizes its lipopolysaccharide in its entire length, which have a rapid reaction of the host's immune system against proteins of the bacterial wall is compromised; consequently, cell lysis is avoided, and this phase is extremely contagious for humans is generated where between 1 and 10 units of this agent already form a human infectious dose. Phase II tends to occur when the bacterium is subjected to subculture processes, which favor a chromosomal deletion that leads to lipopolysaccharide (LPS) being produced incompletely (Vanderburg *et al.,* 2014). Therefore, an antigenic shift occurs because the wall proteins are more accessible to the immune system; it can even be considered avirulent given the rapid inactivation of the agent by the host's complement system (da Costa *et al.,* 2006; Vanderburg *et al.,* 2014). Consequently, in humans, this phase II is mainly related to the manifestation of the acute form of Q fever, associated with symptoms such as pneumonia and hepatitis, contrary to the manifestations reported in immunocompromised patients, where it could favor the development of chronic infection, causing endocarditis and abortions respectively (Cornejo *et al.,* 2020).

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In the context of South America, the information and epidemiology are scarce. The objective of this review is to consolidate the knowledge of the epidemiology of *C. burnetii* in South America. To collect the seropositivity values reported so far in the region, establishing the main manifestations of the infection, analysis of cases, therapies used and the determination of risk factors for this pathogen in the South American context. Additionally, because of the few data presented in the Colombian context, this information is accompanied by the evaluation of Phase II IgG antibodies of *C. burnetii* in a population of 117 in Montelíbano, Córdoba to obtain a current approximation of the epidemiological situation a rural area of the northern region of Colombia.

Materials and Methods

Ethical considerations

This research was approved (Act 126, August 6, 2019) by the ethic committee of the Universidad de los Andes (Bogotá D.C., Colombia), according to the Resolutions 008430 of 1993 and 2378 of 2008. Each patient signed the informed consent and filled a survey about the epidemiological variables.

Information search strategy

This review was performed using PRISMA guidelines. The searches were performed using the in four databases (i.e. PubMed, SciELO, Redalyc and EBSCO). For this, the following word combinations were selected: *Coxiella burnetii* AND the country (Argentina, Chile, Uruguay, Paraguay, Bolivia, Brazil/Brazil, Peru, Ecuador, French Guiana/ French Guiana, Suriname, Guyana/Guiana, Venezuela, and Colombia). For those countries where the spelling of their name differed from Spanish to English, the search string was modified to *C. burnetii* AND (way of writing the name in Spanish OR way of writing the name in English). For the databases that allowed the use of Boolean operators, AND/OR, these were used to carry out the process of filtering articles by country. On the other hand, for those databases that did not allow the use of this operator, the search for *C. burnetii* was carried out accompanied by a manual procedure where the country of interest was selected (Figure 1).

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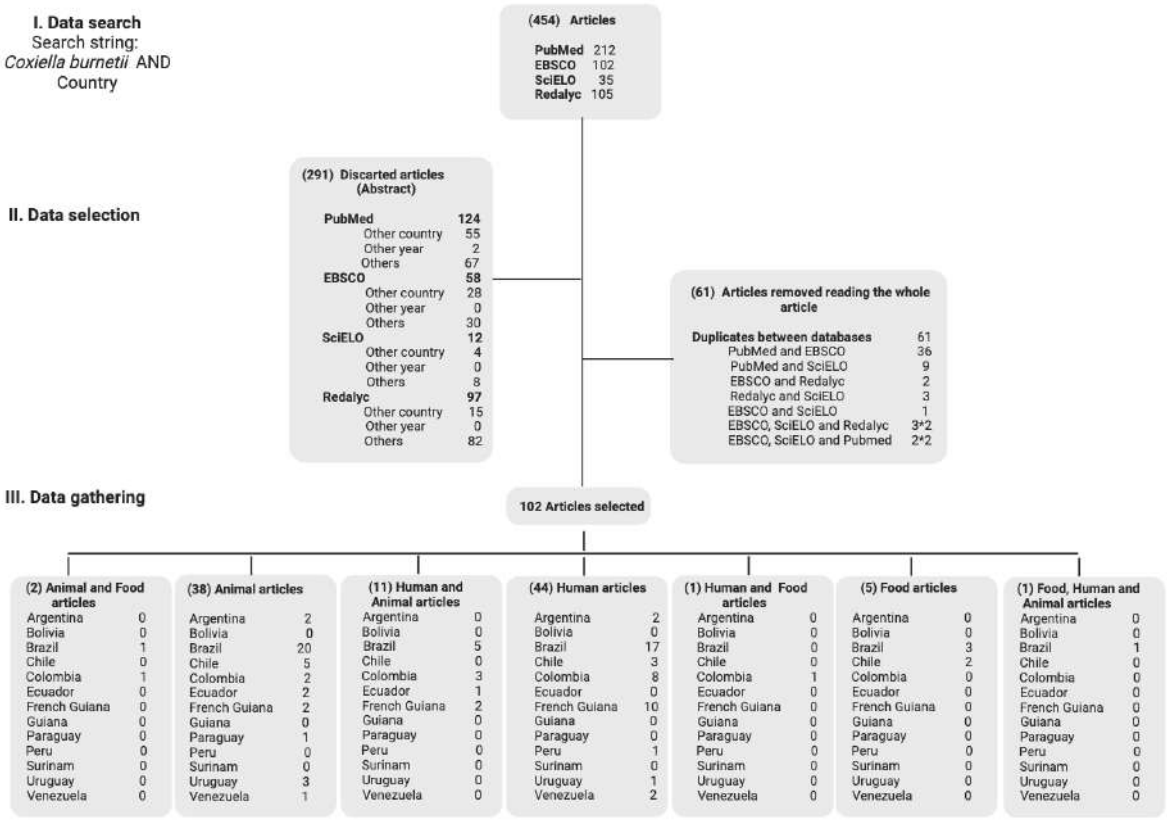

Figure 1. Scheme representation of the methodology used for the systematic review. This is a classification of original research by thematic and country published during 2020-2024.

Selection and data extraction

A reading of the abstracts/summaries of the documents found was performed. The articles were classified according to their title, year of publication, country, database, journal, summary phrase of the article and type of document, such as original article/series of cases /case study/review/systematic review/meta-analysis/book chapter/comparative study. Since the objective of the present analysis of was oriented to *C. burnetii* epidemiology, an exclusion procedure was carried out. For this, i) those articles that did not correspond directly to the country in which the search was carried out were eliminated; ii) articles published before 2000, and iii) those articles that were classified as reviews, systematic reviews, book chapters, incorrect pathogens, journalistic content, strictly microbiological, or therapeutic studies were discarded, theoretical immunology and theoretical epidemiology (Vanderburg *et al.*, 2014). Thus, only articles reporting the epidemiology of *C. burnetii* were included.

Articles with combined language proficiency in English, Spanish, Portuguese, and French were also included.

Selected data

The articles were classified into seven categories: human, animal, food, human and animal, human and food, animal and food and human/animal and food articles. Several aspects were taken into account: epidemiological data reported, population studied, diagnostic tests performed in studies, sample source analyzed, behavior of the infection and infectious disease in humans and animals, analysis of case reports, therapies used to treat the disease in humans, and risk factors associated to the pathogen.

Serological study in Colombia

Cross-sectional study was carried out, where the presence of IgG antibodies was evaluated in blood samples obtained from 177 patients who came for medical care to the E.S.E Hospital Municipal de Montelíbano (province of Córdoba), between September 30th and October 2nd, 2019. The samples were taken, collected, and stored in the Molecular Diagnostic and Bioinformatics Laboratory (Universidad de Los Andes, Bogotá D.C., Colombia). All participants signed an informed consent and filled out a survey of epidemiological variables; then 5ml of blood were collected in tubes without anticoagulant. The samples were centrifuged at 400g × 10 minutes to subsequently separate the serum, and the qualitative determination of IgG antibodies against *C. burnetii* in phase II, an acute manifestation of Q fever, was carried out. This was done using the NovaLisa kit (NovaTec Immunodiagnostica GMBH, Dietzenbach, Germany) where each sample was read at absorbance values of 450 and 655 nm and interpreted based on the value of nephelometric turbidity units (NTU), according to the manufacturer's instructions. In this way, the sera were considered positive if the magnitude of NTU>11, doubtful if 9 NTU 11 and negative if NTU <9.

Results

Epidemiological analysis in humans

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For the epidemiological analysis studies reported in humans in South America, a total of 57 articles associated with nine countries (i.e. Argentina, Brazil, Chile, Colombia, Ecuador, French Guiana, Peru, Uruguay and Venezuela) were identified, which recorded different values with respect to the data from seropositivity (Table 1). Argentina presented ranges from 0.00 to 1.00%, Brazil 0.00 to 100.00%, Chile 0.72 to 20.00%, Colombia 0.00 to 100.00%, Ecuador 34.00%, French Guiana 0.0017 – 100.00%, Peru 9.00%, Uruguay 37.00% and Venezuela 5.31 to 8.90%. In Bolivia, Guyana, Paraguay and Suriname there were no articles of epidemiological reports, may be a consequence of the low number of articles focused on this pathogen in the countries of interest. The variability of clinical manifestations, non-specific symptoms and the fact that many of the countries in South America do not present mandatory notification of this pathogen neither in humans nor in animals (Eraso-Cadena *et al.,* 2018).

Among the samples analyzed, serum was the most common, with 85.96% (49/57) of the articles analyzing serum. Other possible samples included blood, bronchoalveolar lavage, valves, tomography scans and faecal samples (Supplementary Appendix). The 77.19% of the articles (44/57) were population studies, while 22.81% (14/57) focused on case studies.

The difference in seropositivity levels between populations exposed and not exposed to these agents is highlighted. While general community studies showed lower seroprevalence levels, populations such as farmers, soldiers, police, patients with immunosuppression and rural populations showed levels to be considered. Studies analyzing seroprevalence in patients with suspected dengue, with seroprevalences ranging from 3.30% to 21.40% (Mares-Guia *et al.,*. 2016; França *et al.,* 2022; Meurer *et al.,* 2022), and patients with endocarditis, acute febrile syndrome and pneumonia as populations to be considered for diagnosis of this pathogen, stand out.

Finally, the association of the chronic form of Q fever and immunosuppression, an analysis of HIV patients was carried out. This study showed that of 125 patients, 3.20% (n=4) were positive for phase I antibodies to *C. burnetii* (Lamas *et al.,* 2009). This could suggest an association between the chronic form of Q fever and immunosuppression, although the prevalence is still controversial given the lack of studies.

Table 1. Comparative seropositivity percentages among humans and animals by country.

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Country	Human articles	Animal articles
Argentina	0.00 –1.00%	15.4 – 44.6%
Bolivia	–	–
Brazil	0.00 – 100.00%	0.00 – 100.00%
Chile	0.72 – 20.00%	0.00 – 100.00%
Colombia	0.00 – 100.00%	0.60 – 61.60%
Ecuador	34.00%	12.60 – 52.90%
French Guiana	0.0017 – 100.00%	0.00 – 100.00%
Guiana	–	–
Paraguay	–	45.00%
Peru	9.00%	–
Surinam	–	–
Uruguay	37.00%	0.00 – 100.00%
Venezuela	5.31 – 8.90%	60.63%

Epidemiological analysis in animals

In relation to the epidemiological studies reported in animals, 52 articles associated with nine countries was identified: Argentina, Brazil, Chile, Colombia, Ecuador, French Guiana, Paraguay, Uruguay, and Venezuela; where seropositivity, as in human articles, was variable according to the region analyzed. These data show the circulation of *C. burnetii* in South America, infection by this agent was identified in 14 different organisms (Figure 2).

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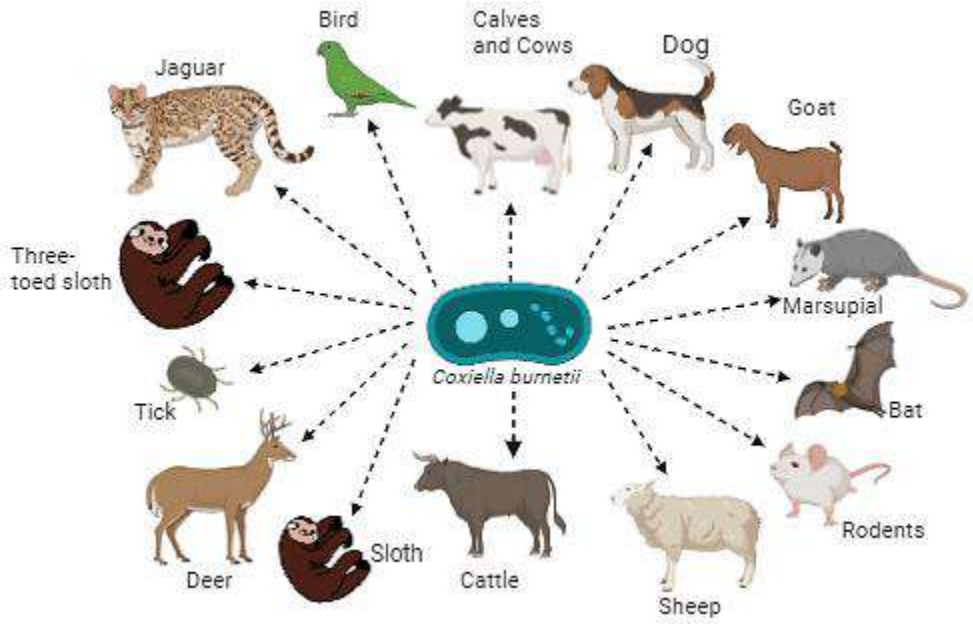

Figure 2. Reported *C. burnetii* infections across diverse animals in South America. Figure made in Biorender (https://biorender.com/).

In South America, *C. burnetii* infection was evidenced in wild and domestic animals, such as bats, birds, cattle, cows, deer, dogs, goats, jaguar, marsupials, rodents, sheep, sloth, three-toed sloth and ticks. Among the samples analyzed, it was found serum, organs, tissues, eggs, fetuses, blood, placenta, stool, bronchoalveolar lavage, vaginal and anal mucus and larvae or the animal in small animals like ticks (Supplementary Appendix). It is important to note that in various animals, the cut-off titers are not well defined and vary according to studies (Cicuttin *et al.,* 2013). Mioni *et al.,* performed quantification of three positive samples in cattle showed a concentration of *C. burnetii* that ranged from $5.69\ X\ 10^2$ to $4.57\ X\ 10^4$ bacteria/mL, with the pathogen being found in different tissues, which would indicate a generalized distribution of bacteria during infection (Mioni *et al.,* 2022).

Epidemiological analysis in food

The seroprevalence of the pathogen found in food in Brazil were (4.60 to 100.00%), Chile (2.10-76.00%) and Colombia (6.00-45.00%), which report positive samples of *C. burnetii* DNA in products such as bovine/sheep/goat milk (7 studies) and cheeses (2 studies) (Supplementary Appendix). This may suggest a possible route of oral transmission of this

pathogen that should be considered. According to the association of raw dairy products and *C. burnetii* infection, the study by Rozental *et al.,* (2020) where about five samples (9.4%) with genetic material of *C. burnetii* in cheese (artisanal cheese from Minas, MAC) were registered. Situation of great interest because of the 16.2 tons produced daily from artisanal cheese, 10% or 1.62 tons/day could be contaminated with this pathogen (Rozental *et al.*,2020). It should be considered that samples with negative results for *C. burnetii* are truly free of the pathogen, since detection techniques for *C. burnetii* in these products have not been fully standardized (Contreras *et al.,* 2015). In addition, for oral transmission the infective dose has not been documented yet and recent articles have suggested which may be higher than the inhalation dose (1-10 bacteria) (Zanatto *et al.,* 2019b).

Clinical manifestations in humans

Most *C. burnetii* infections are usually self-limited, however, on some occasions they can progress to more severe infections with acute manifestations or development of chronic phases. Regarding acute Q fever, according to the literature, about 40% of individuals infected with *C. burnetii* will develop this presentation, which evolves mainly in three forms: flu-like syndrome, hepatitis, and pneumonia (Rozental *et al.,* 2012; Orrego *et al.,* 2020). The latter is recorded as the most common presentation; countries such as French Guiana have stablished about 24% of cases of acquired pneumonia related to *C. burnetii* (Edouard *et al.,* 2014).

This acute manifestation may also be accompanied by other symptoms such as myalgia, encephalitis, aseptic meningitis, headache, anorexia, high and prolonged fever, asthenia, dry cough, respiratory condition, general malaise, pleuritic chest pain, rash, pericarditis, myocarditis, and infiltrates that are visible on chest radiographs (Rozental *et al.,* 2012; Echeverría *et al.,* 2019; Von Ranke *et al.,* 2019). Deaths are rare and usually when they do occur, they are associated with poor health conditions, such as immunosuppression of the patient (Rozental *et al.,* 2012) or related with the circulating genotype. In French Guiana a specific strain MST17, genotype 17, genotype associated with the QpH1 plasmid, has been reported to cause the most severe clinical forms of acute Q fever in experimental animal models due to its tropism to the lungs. MST17 is considered one of the most pathogenic *C. burnetii* strains worldwide (Mahamat *et al.,* 2013; des Vaux *et al.,* 2024).

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Contrary to this situation, for the chronic phase of Q fever the literature establishes that less than 5 % of infected individuals will progress to this manifestation, some estimates even report approximately 2% (Echeverría *et al.,* 2019; Orrego *et al.,* 2020). This chronic presentation is the result of the persistence of the pathogen after a primary infection, which can occur months or years after an acute infection, that is, a time after which patients generally cannot remember the source of exposure, thus making diagnosis difficult of the disease (Echeverría *et al.,* 2019; Von Ranke *et al.,* 2019).

The most common presentation of this phase is usually endocarditis, about 60 to 70% of cases with chronic Q fever will develop this cardiac infection (Cornejo *et al.,* 2020); however, this is commonly associated with previous conditions of the patient such as valve disease and immunosuppression (Rozental *et al.,* 2012). On the other hand, it has been reported that chronic Q fever can be related to other symptoms, signs, and laboratory findings such as vascular infection, prosthetic arthritis, persistent fatigue, lymphadenitis, and less common manifestation such as granulomatous lesions in the bones, lungs, and liver, joints, testes, and soft tissues (Rozental *et al.,* 2012; Echeverría *et al.,* 2019; Orrego *et al.,* 2020). Pulmonary affectations, although they are mainly associated with the acute presentation of this pathology, have occurred in some cases where patients establish extrapulmonary manifestations accompanied by intense headache, myalgia and joint pain in the chronic manifestation of Q fever (Rozental *et al.,* 2012).

Clinical manifestations in animals

Although the infection may be subclinical, one of the most common manifestations is spontaneous abortion. This is a product of the preferential location of the bacteria in the uterus, mammary glands and placenta (Oropeza *et al.,* 2010). This relationship of abortions with *C. burnetii* has been documented in dogs, cats, sheep, cows, and goats; being this last animal of great relevance since great susceptibility has been registered (Oropeza *et al.,* 2010; Cicuttin *et al.,* 2013; Pacheco *et al.,* 2013; de Oliveira *et al.,* 2018; Changoluisa *et al.,* 2019; Zanatto *et al.,* 2019b). Additionally, some authors have established an association of coxyellosis with premature death of infected animals, endometritis, mastitis, and infertility (Cicuttin *et al.,* 2013; Zanatto *et al.,* 2019a). Other authors have even established a

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relationship of *C. burnetii* with infectious rhinotracheitis, viral diarrhea and anorexia in cows (Macías-Rioseco *et al.,* 2019).

Case reports

To explore how these symptoms and diseases are presented, an analysis of the individual cases registered was carried out. For human patients with pneumonia, 5 case report articles were found (Meza & Rosso, 2012; Meza; Baret *et al.,* 2012; Rozental *et al.,* 2012; Von Ranke et al, 2019; Mattar *et al.,* 2014). The most common symptoms among these patients were fever, chills, abdominal pain, fatigue, respiratory compromise, and muscle weakness (Baret *et al.,* 2001; Rozental *et al.,* 2012). The majority of cases had ill-defined opacities on chest radiograph, increased bilateral pulmonary infiltrates. Diffuse skin lesions were observed in one case (Meza & Rosso, 2012). Laboratory findings identification of pulmonary infiltrates, renal failure, thrombocytopenia, hypoxia, liver disorders, leukocytosis with neutrophilia and elevated markers of inflammation (Rozental *et al.,* 2012; Eraso-Cadena *et al.,* 2018). Also, Baret *et al.,* (2001), carried out an analysis between patients with pneumonia due to *C. burnetii* and pneumonia owing to another causative agent. Regarding the above, it was found that pneumonia because of *C. burnetii* generally presents more severely, with chills, sweating, headache, joint pain and high levels of C-reactive protein in the blood mainly. On the other hand, symptoms and signs such as body temperature greater than 38.5°C, respiratory symptoms, radiographic signs, and lymphocyte count, platelets, and liver enzyme levels did not differ between groups. However, these latter symptoms, signs, and laboratory findings are not specific to the diagnosis of *C. burnetii* pneumonia.

Four reports of a human patients with endocarditis were recorded. These patients were characterized by presenting symptoms such as intermittent fever, chills, general weakness, fatigue, musculoskeletal pain, headache, blurred vision, weight loss, cough, dyspnea, orthopnea and decreased urinary output (Siciliano *et al.,* 2008; da Cruz *et al.,* 2013; Mahamat *et al.,* 2013; Mizuta *et al.,* 2022).

Finally, four articles described case reports where patients did not yet report association with pathologies such as pneumonia or endocarditis (da Costa *et al.,* 2006; Lemos *et al.,* 2011; de Lemos *et al.,* 2018; Uribe *et al.,* 2021). The most common symptoms included abdominal pain, fatigue, and respiratory compromise. Two cases reported fever and one rash (de Lemos

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et al., 2018; Uribe *et al.,* 2021. Laboratory tests were characterized by pulmonary involvement, such as edema and breath sounds, cardiac involvement and leukocytosis with neutrophilia (da Costa *et al.,* 2006; Lemos *et al.,* 2011; de Lemos *et al.,* 2018; Uribe *et al.,* 2021).

Treatment of the disease

For the treatment of Q fever, different therapies based mainly on ciprofloxacin, cephalosporins, gentamicin, vancomycin, chloroquine, amoxicillin, clavulanic acid, azithromycin, meropenem, levofloxacin, rifaprim, and amphotericin has been registered (Baret *et al.,* 2001; Siciliano *et al.,* 2008; Lemos *et al.,* 2011). Nevertheless, since *C. burnetii* has reported resistance to antibiotics generally used empirically, especially for the treatment of endocarditis with negative blood cultures, such as b-lactams and aminoglycosides, when this pathogen is suspected as the causative agent of the pathology of the patient proceeds to carry out a treatment mainly with doxycycline (Máttar and Parra, 2006). These therapies can be monotherapy, only with doxycycline (Baret *et al.,* 2001) or associated with other antibiotics such as doxycycline+chloroquine, doxycycline+levofloxacin and doxycycline+ciprofloxacin (Siciliano *et al.,* 2008).

According to Siciliano *et al.,* (2008) doxycycline+chloroquine treatment has been established to be the shortest and most effective therapy for severe manifestations (18 months), however, this treatment requires constant monitoring due to its ocular toxicity. In addition to this, it has been recorded that if the latter antibiotic, chloroquine, is not available, ciprofloxacin can be used but with a treatment extension of 72 months. Furthermore, the treatment doxycycline+fluoroquinolone (levofloxacin-namacrol) is an alternative treatment for this pathology, although it may require extended therapies of up to 4 years.

Finally, mono-therapeutic schemes with macrolides have also been reported, which presents an initial response, but with their suspension there is a high risk of recurrence (Siciliano *et al.,* 2008). Therefore, since *C. burnetii* presents resistance to beta-lactams and aminoglycosides, most articles recommend targeted therapy with antibiotics to which susceptibility has been evidenced, such as rifampicin, tetracyclines, and fluoroquinolones, being the best alternative in doxycycline treatment normally with two doses of 100 mg per day for a time between 14 days to 18 months according to the manifestations presented by

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the patient (Baret *et al.,* 2001). For those individuals who do not tolerate doxycycline, macrolide or fluoroquinolone therapy has been established as an alternative.

Diagnosis techniques

The methods that allow the direct detection of the microorganism of interest, such as cell culture and the polymerase chain reaction (PCR), turn out to be the most appropriate techniques for diagnosis; in South America, the tools or specialized laboratories, to carry out these tests does not they be always available. Especially cell culture which is a risky, expensive, difficult and ineffective procedure for *C. burnetii* given the difficulty to isolate this microorganism in cell lines, which is why serological alternatives are usually more easily used. In South America, the studies carried out in humans and animals registered serology as the most used technique (64.91% and 40.38% respectively) (Figure 3).

Serological analyzes are characterized by being simple and fast methodologies that allow the researcher to discriminate between primary and secondary infections and obtain approximations to the phase of the patient's disease; this, according to the isotype of immunoglobulin and antigen analyzed respectively. It is important to highlight that this type of test is subject to interference such as possible cross-reactions with bacteria of the genera *Bartonella*, *Rickettsia*, and *Legionella* (Blair *et al.,* 2004; Mares-Guia *et al.,* 2016; De Lemos *et al.,* 2018). To avoid the above situation, a considerable proportion of articles carried out combined analyzes of molecular techniques. Contrary to studies in humans and animals, for the category of food articles, the most used diagnostic technique was PCR and variants (100%) (Figure 3).

A study by Mattar *et al.,* (Mattar *et al.,* 20214) compared three serological methods for the evaluation of *C. burnetii* antibodies: commercial IFA, in house IFA and ELISA. It showed a good agreement between commercial and in house IFA while ELISA showed high specificity but low sensitivity. As the use of complete antigens in serodiagnosis can lead to cross-reactivity with other related proteobacteria, the study by Fontes *et al.,* (Fontes *et al.,* 2021) showed that some *Coxiella*-like bacteria belonging to clades A and C produce positive PCR results when tested with primers initially thought to be specific for *C. burnetii*. This situation highlighted the need for further studies and common techniques to identify these pathogens.

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In addition to the differences in seropositivity cut-offs between articles, which may influence the diagnosis of disease.

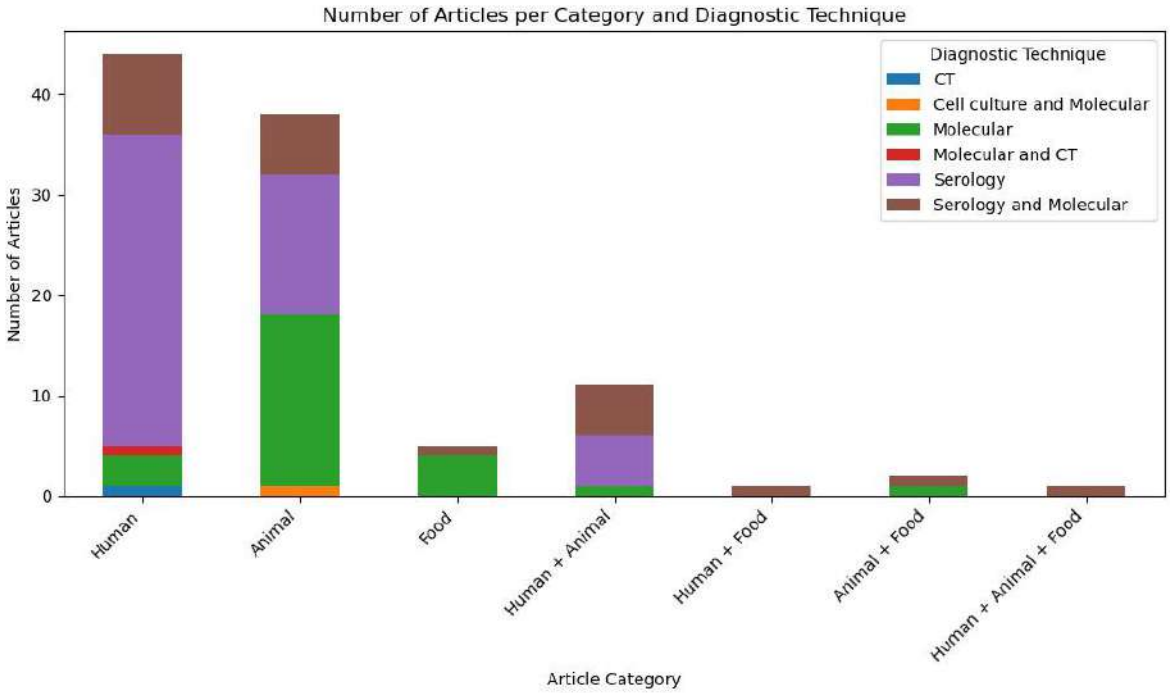

Figure 3. Diagnostic techniques used across studies.

Finally, since many of the studies associated with acute Q fever established the presence of visible infiltrates on chest radiographs as a diagnostic approach, the study by Von Ranke *et al.*, (2019) where the main patterns in the study of high-resolution computed tomography (HRCT). According to this article, it was found that the main patterns consist of ill-defined opacities on the chest radiograph, where consolidations and nodules with halos of opacity occur late in the disease, in the early stages the radiographs may be normal. Nevertheless, although these irregular contours and halos of opacity are present, pneumonia caused by Q fever cannot be differentiated from pneumonia caused by another agent based on radiographic findings alone.

Risk factors

Among the possible risk factors, the occupational risk is in the first place, that is, individuals who present a high degree of close contact with animals and their different products such as

veterinarians, farmers and slaughterhouses (Mattar *et al.,* 2015; De Lemos *et al.,* 2018). Likewise, studies carried out in patients positive for Q fever in South America showed that seropositivity is higher in young adults, immunosuppressed patients and individuals who reported a history of tick bites, cattle slaughter, longer exposure time to cattle and living with animals such as chickens, dogs, cats, sheep and capybaras (Lamas *et al.,* 2009; Cicuttin *et al.,* 2015; Mares-Guia *et al.,* 2016; Eraso-Cadena *et al.,* 2018; Molina-Guzmán *et al.,* 2019; Orrego *et al.,* 2020). Davoust *et al.,* (2014) suggested a possible association for contact with feces due to the favoring of the transmission of *C. burnetii* by aerosols. In addition, the study by Gardon *et al.,* (2001) suggested as other relevant factors: living near a forest, frequent sighting of wild mammals and individuals with air-conditioned vehicles.

In relation to the potential risk factors associated with animals, studies carried out on goats evidenced intensive farming as a relevant factor; in sheep, male sex and location were established (de Souza *et al.,* 2018) and in cattle, higher prevalence in individuals older than 4 years and females (Carbonero *et al.,* 2015). Regarding the association with abortion and *C. burnetii* seropositivity, the study by Changoluisa *et al.,* (2019) found no relationship. Regarding the risk factors for food contamination, these are not yet clear since the study by Betancur-Jiménez *et al.,* (2015) establishes that there is no significant association between seropositivity and variables such as consumption of raw milk or contacts with birth products, while Siciliano *et al.,* (2006) suggest milk consumption is not considered a potential risk behavior.

Seropositivity in patients from a Colombian rural area

Of the 177 blood samples analyzed, the samples were collected in 2019 at hospital of Montelibano (Córdoba, Colombia), all participants signed a consent approving the use of their sample (ethics committee of the Universidad de los Andes, Bogotá D.C., Colombia). 71.2% corresponded to women, the majority was a mixed-race population (73.4%) and contact with animals (61%). Of these samples, 8 were reported to be positive for Phase II IgG antibodies (acute manifestation of Q fever) to *C. burnetii.* This represents a seropositivity of 4.5% (Table 2). It was evidenced that of the eight people who reported Phase II IgG antibodies, seven corresponded to women and 75% registered contact with intra- and peridomiciliary rodents; as well as the fact that 62.5% registered contact with animals.

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This could suggest a relevant role of rodents in the transmission of the bacteria to humans and that women are more exposed to infection by this agent. However, it is necessary to performed new studies to characterize the behavior of the infection in Colombia. Finally, it is emphasized that one of the patients who registered a positive sample of IgG antibodies against *C. burnetii* in previous articles also showed IgG antibodies to arenavirus; fact that, although it does not show a coinfection of *C. burnetii* and arenavirus because a current infection is not being analyzed.

Table 2. Description of the sociodemographic variables of the studied population.

Variables	Categories	N	%	Mean
Age	–	177	100	41.3
Gender	Female	126	71.2	41.2
	Male	51	28.8	41.5
Race	African - American	47	26.65	–
	Mixed - race	130	73.5	–
Indoor rodents	Yes	100	56.5	–
	No	77	43.5	–
Peridomiciliary rodents	Yes	99	55.9	–
	No	78	44.1	–
Drinking water	Yes	141	79.7	–
	No	36	20.3	–
Aqueduct	Yes	141	79.7	–
	No	36	20.3	–
	Yes	39	22	–
Presence of ectoparasites	No	135	76.3	–
	NA	3	1.7	–
Garbage collection	Yes	154	87.01	–
	No	23	13	–
Contact with animals	Yes	108	61	–
	None	69	39	–

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	Housekeeper	61	34.5	–
	Farmer	12	6.8	–
Occupation	Student	16	9.	–
	Health care field	14	7.9	–
	Others	54	30.5	–
	NA	20	11.3	–

NA: Not applicable

Discussion

The reviewed studies show the circulation of *C. burnetii* in South America, mainly in countries such as Argentina, Brazil, Chile, Colombia, Ecuador, French Guiana, Paraguay, Peru, Uruguay, and Venezuela. It is noteworthy that the percentage of seropositivity or seroprevalence was variable depending on the country studied and whether the studies were carried out in humans or animals. Brazil and French Guiana were countries that registered the highest levels of seropositivity in both humans and animals, a situation that may be associated with close contact with animals due to livestock production. In the case of countries such as Bolivia, Guyana and Suriname, the circulation of the pathogen cannot be ruled out since no articles associated with epidemiological data were registered in the region. Regarding the diversity of animals that have registered infection in South America, it is established that around there are a high diversity of animals susceptible to infection by this bacterium (Figure 2). Ruminants are the main reservoir, but the role of ticks and bats in the region cannot be overlooked, as they may be facilitating the widespread and rapid transmission of the bacteria to humans (Almeida *et al.*, 2012; Ferreira *et al.*, 2018). Currently, more than 40 species of ticks can be infected with *C. burnetii*, demonstrating the role that these vectors may be playing in the transmission to wild and domestic vertebrates, it is worth highlighting the role of rodents since they can transmit to humans (Machado-Ferreira *et al.*, 2016; de Oliveira *et al.*, 2018).Similarly, *C. burnetii* infection in bats (order Chiroptera) also requires special attention. Animals belonging to this order are recorded on all continents, except Antarctica, and are distinguished by their high degree of interaction with humans and

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other animals due the formation of colonies that group diversity of individuals of reproductive age (Ferreira *et al.*, 2018).

Regarding food analysis, it has been demonstrated that *C. burnetii* has been found in products such as milk and cheese (artisanal cheese from Minas, Brazil), which emphasizes constant surveillance in these products. Although it has been documented that the main source of transmission of *C. burnetii* to humans is through aerosols or contaminated particulate material, epidemiological evidence suggests a relationship between exposure to raw dairy products and infection with this microorganism. Situation of great relevance in South America given reports in countries such as Brazil where unpasteurized milk consumption is recorded near 30.00% and the fact that the milk sold illegally is approximately 900 million liters per year (Rozental *et al.,* 2020).

Given that infectious diseases continue to be the cause of high rates of morbidity and mortality in South America, they remain the main reason for consultations in hospital emergency departments and outpatient settings (Mahamat *et al.,* 2013). It can be determined that the situation of *C. burnetii* does not contribute to improving this scenario, presenting a great challenge because this agent often goes undiagnosed due to uncommon diagnosis and being easily confused with other infectious agents present in the region, such as dengue and chikungunya. Pathologies like Q fever remain undiagnosed, exacerbating the problem (Rozental *et al.,* 2012; Eraso-Cadena *et al.,* 2018). Different areas of South America have been considered endemic regions for dengue, rickettsiosis of the spotted fever group (SFG), chikungunya and zika, which a are pathologies whose symptoms overlap with clinical pictures of Q fever, and it is also common that the laboratory diagnosis not to be performed (Mares-Guia *et al.,* 2016).

Besides being asymptomatic in most cases, Q fever can present in both chronic and acute phases, with the acute phase being the most registered presentation among the South American population. The chronic manifestation is mainly linked to the progression of the pathogen in the infectious process or conditions of immunosuppression in the patient. The acute phase of Q fever is known to evolve mainly towards three forms: flu-like syndrome, hepatitis, and pneumonia. However, in South America, an association has been established mainly between this manifestation and pneumonia accompanied by symptoms such as fever, chills, abdominal pain, fatigue, respiratory compromise, and muscle weakness.

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In contrast, the chronic phase of Q fever most commonly presents as endocarditis, accompanied by symptoms such as intermittent fever, chills, general weakness, fatigue, musculoskeletal pain, headache, blurred vision, weight loss, cough, dyspnea (shortness of breath), orthopnea (difficulty breathing when lying down), blood in the urine, and decreased urine output. Laboratory tests have also shown retinal hemorrhage, anemia, hematuria, proteinuria, low complement levels, pulmonary edema (abnormal accumulation of fluid in the lungs), and aortic insufficiency in affected individuals. Although these findings may be subject to variations with respect to the individual's own health conditions and age, there is need to consolidate the specific or most common symptoms for Q fever, such as those reported in the study conducted by Baret *et al.*, (2001). It was established that *C. burnetii* in this study that pneumonia tends to present more severely, with chills, sweating, headache, joint pain and high levels of C-reactive protein in the blood. In addition to this, it is suggested to accompany the laboratory studies with previous surveys where it can be related if the individual had contact with cattle.

Regarding the situation with animals, it has been established that the manifestations in this group can range from abortions to premature deaths of infected animals, endometritis, mastitis, infertility and infectious rhinotracheitis, viral diarrhea and anorexia in cows; these manifestations that translate into significant economic losses and ratify the relevance of studying this circulating pathogen in the territory. Most articles establish doxycycline as the treatment of choice, although, to reduce the time of these therapies, it is possible to resort to accompanying other antibiotics such as chloroquine and hydroxychloroquine.

The diagnostic techniques most used in the articles analyzed were the serological techniques, because of their rapidity and ease in development, this approach is highly relevant because it enables to distinguishing between a current or recent infection and monitoring if the pathogen is generating affectations again, increasing IgG titers four times (Rozental *et al.*, 2012). However, since cross reaction with other genera such as *Bartonella*, *Rickettsia*, and *Legionella* can occur, it is recommended to use combined diagnostic techniques, where serological studies are accompanied by other test type, such as molecular (preferably PCR). For acute Q fever, the best alternative is to perform PCR during the first two weeks after the symptom’s onset, and prior to administering antibiotics; If antibody-based reporting is being used, it is suggested to perform the analysis after the third week of symptom onset since most

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individuals with Q fever convert in the third week post-infection (Baret *et al.,* 2001; Lamas *et al.,* 2013).

Based on the observations made, it is suggested that in humans, the main risk factors for Q fever include having contact with animals, prolonged exposure to cattle, association with cattle slaughter, contact with feces, tick bites, immunosuppression, being a young adult, occupational exposure, and even living in a place with air conditioning in cars, which can be a relevant source of infection. In animals, the main risk factors proposed include intensive breeding, male sex, and location in sheep, and in bovines, advanced age and being female. However, since most of these articles did not consider random analysis, the risk factors may be biased towards the studied population.

Nonetheless, concerning the situation in Colombia, the ELISAs carried out registered a seropositivity of 4.5% for the population analyzed in Montelíbano, Córdoba. This magnitude is close to that registered by the study by Molina-Guzmán *et al.,* (2019), where individuals dedicated to livestock in San Pedro de los Milagros (province of Antioquia), were analyzed finding 2.3% IgG antibodies to *C. burnetii*. This suggests the circulation of the pathogen in Colombia, particularly if one considers previous studies conducted in the region around the year 2003, where Mattar and Parra (Máttar and Parra, 2006) registered a seropositivity of 23.6% in individuals from Córdoba and Sucre. For this reason, a scenario is presented where this zoonotic disease could be prevalent among residents of the Caribbean area, possibly due to their close contact with livestock.

To conclude, *Coxiella burnetii* is a microorganism present in South America, which may be behaving as a real and underestimated threat to the health systems of the region. Reports on its epidemiology suggest variable seropositivity within the region and between reports in humans and animals. Its infection in both humans and animals that compromise the quality of life and animals that compromise the quality of life of the organism and generate large economic losses. For this reason, it should be included in the differential diagnosis of diseases in the region. In risk factors are not yet clear, but it is suggested that profession, contact with animals, place of residence, and animal husbandry are factors to be considered. For this reason, a greater number of studies on its epidemiology and follow-up are recommended to characterize the transmission, presence and risk of this agent in the region.

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Declarations

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Conflict of interest

The authors declare that they have no conflict of interest.

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Authors contribution

Andrea K. Alvarez-Osorio: Database search, information review, serological assay, and manuscript preparation. Miguel H. Parra: Information review, supervision of serological assay, and final version manuscript correction. Carolina Montoya-Ruiz: Information review, supervision of serological assay, manuscript preparation, translation, and final version correction.

Use of artificial intelligence (AI)

No AI or AI assisted technologies were used during the preparation of this work.

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