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Revista Colombiana de Ciencias Pecuarias

Literature Review

# Epidemiological situation of *Coxiella burnetii* infections in South America: A systematic review

## *Situación epidemiológica de las infecciones por Coxiella burnetii en América del Sur: Una revisión sistemática*

## *Situação epidemiológica das infecções por Coxiella burnetii na América do Sul: Uma revisão sistemática*

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**To cite this article:**
Alvarez-Osorio AK, Parra MH, Montoya-Ruíz C. Epidemiological situation of Coxiella burnetii infections in South America: A systematic review. Rev Colomb Cienc Pecu. 2025; 38(3):e357454. DOI: https://doi.org/10.17533/udea.rccp.e357454

**Received:** June 13, 2024
**Accepted:** January 31, 2025.
**Published:** July 16, 2025.

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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 undergoes antigenic variation between 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 mammalian species, including humans. **Objective:** Due to the limited information available on this pathogen in South America, we conducted a systematic review of its epidemiology between 2000 and 2024 to consolidate data. Additionally, this review was complemented by an assessment of the presence of IgG Phase II antibodies in a population of 117 people in the province of Córdoba, Colombia. **Results:** Epidemiological studies confirmed the presence of this pathogen in humans, animals, and even food sources, with seropositivity rates varying by region. Notably, most registered human cases were associated with the acute phase, while animal cases were predominantly linked to reproductive disorders. The evaluation of IgG Phase II antibodies in the Córdoba population indicated a seropositivity rate of 4.52%. **Conclusion:** These findings underscore the reality that *C. burnetii* poses a significant and possibly underestimated threat in Latin 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, una enfermedad zoonótica que afecta tanto a humanos como a animales. Esta bacteria 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 neumonía y hepatitis, y puede afectar a diversas especies de mamíferos, incluido el ser humano. **Objetivo:** Con el fin de consolidar la información sobre este patógeno en Suramérica, se realizó una revisión sistemática de artículos publicados entre los años 2000 y 2024. Además, esta revisión fue complementada con una evaluación de la presencia de anticuerpos IgG Fase II en una población de 117 personas de Córdoba, Colombia. **Resultados:** Los estudios epidemiológicos confirmaron la presencia de *C. burnetii* en humanos, animales e incluso en alimentos, con tasas de seropositividad variables según la región. Los estudios en humanos asociaron principalmente la infección con la fase aguda, mientras que los casos en animales se relacionaron predominantemente con problemas reproductivos. La evaluación de anticuerpos IgG Fase II en la población de Córdoba mostró una seropositividad del 4,52%. **Conclusión:** Estos resultados evidencian que *C. burnetii* representa una amenaza significativa y posiblemente subestimada en Latinoamérica y Colombia.

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

**Resumo**

**Antecedentes:** *Coxiella burnetii* é o agente causador da febre Q, uma doença zoonótica que afeta tanto humanos quanto animais, apresentando variação antigênica 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, podendo afetar diversas espécies de mamíferos, incluindo o ser humano. **Objetivo:** Para consolidar as informações sobre esse patógeno na América do Sul, foi realizada uma revisão sistemática de artigos publicados entre os anos 2000 e 2024. Além disso, esta revisão foi complementada com uma avaliação da presença de anticorpos IgG Fase II em uma população de 117 pessoas da província de Córdoba, Colômbia. **Resultados:** Os estudos epidemiológicos confirmaram a presença de *C. burnetii* em humanos, animais e até mesmo em alimentos, com taxas de soropositividade variáveis conforme a região. Os estudos em humanos associaram principalmente a infecção com a fase aguda, enquanto os casos em animais estavam predominantemente relacionados a problemas reprodutivos. A avaliação de anticorpos IgG Fase II na população de Córdoba indicou uma soropositividade de 4,52%. **Conclusão:** Esses resultados demonstram que *C. burnetii* representa uma ameaça significativa e possivelmente subestimada 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 serves as the etiological agent of Q fever. It is a small bacillus (0.30-1.00 µm) (Eraso-Cadena et al., 2018). This bacterium is primarily transmitted as a zoonotic agent, mainly through inhalation and contact with biological substances such as urine, feces, milk, and placental products from infected animals (Eraso-Cadena et al., 2018). Another relevant characteristic of this microorganism is its ability to undergo antigenic variation (da Costa et al., 2006).

In Phase I, the bacterium synthesizes a complete lipopolysaccharide (LPS), which limits the host immune system's ability to recognize bacterial wall proteins. Consequently, cell lysis is avoided, and this phase is highly contagious to humans, with as few as 1 to 10 bacterial units constituting an infectious dose. Phase II occurs when the bacterium undergoes subculture, leading to a chromosomal deletion that results in incomplete LPS production (Vanderburg et al., 2014). As a result, an antigenic shift occurs, making bacterial wall proteins more accessible to the immune system. This phase may even be considered avirulent due to the rapid inactivation of the bacterium by the host's complement system (da Costa et al., 2006; Vanderburg et al., 2014).

In humans, Phase II is primarily associated with the acute form of Q fever, which presents symptoms such as pneumonia and hepatitis. However, in immunocompromised individuals, it may contribute to the development of chronic infection, leading to conditions such as endocarditis and abortion (Cornejo et al., 2020).

In South America, epidemiological data on this pathogen are scarce. The objective of this review is to consolidate knowledge regarding the epidemiology of *C. burnetii* in the region by collecting reported seropositivity values, identifying the main clinical manifestations, analyzing case reports, evaluating therapeutic approaches, and determining risk factors associated with this pathogen in the South American context. Additionally, due to the limited data available in Colombia, this review is complemented by an evaluation of *C. burnetii* Phase II IgG antibodies in a population of 117 individuals from Montelíbano, Córdoba, providing a current approximation of the epidemiological situation in a rural area of northern Colombia.

## Materials and Methods

### *Ethical considerations*

This research was approved (Act 126, August 6, 2019) by the ethics committee of the Universidad de los Andes (Bogotá D.C., Colombia), in accordance with Resolutions 008430 of 1993 and 2378 of 2008. Each patient signed an informed consent form and completed a survey on epidemiological variables.

### *Information search strategy*

This review was performed using the PRISMA guidelines. Searches were conducted in four databases (PubMed, SciELO, Redalyc, and EBSCO). For this purpose, the following search terms 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 countries where the spelling of their name differs between Spanish and English, the search string was adjusted to *C. burnetii* AND (country name in Spanish OR country name in English). For databases that supported Boolean operators (AND/OR), these were applied to refine the article selection by country. Conversely, for databases that did not allow the use of Boolean operators, the search for *C. burnetii* was performed manually, selecting the country of interest (Figure 1).

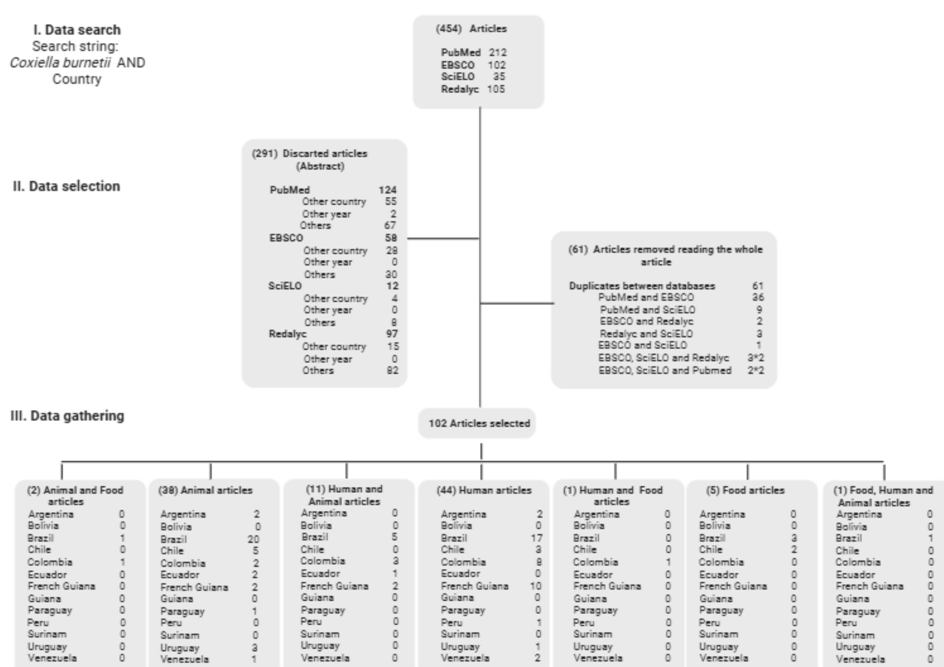


**Figure 1.** Schematic representation of the methodology used for the systematic review. This figure classifies original research by theme and country, published between 2020 and 2024.

### *Selection and data extraction*

A preliminary review of the abstracts of the retrieved documents was conducted. Articles were classified based on title, year of publication, country, database, journal, summary of the article, and document type (original article, case series, case study, review, systematic review, meta-analysis, book chapter, or comparative study).

Since this analysis focused on the epidemiology of *C. burnetii*, an exclusion process was applied:

i) Articles that were unrelated to the country of interest were excluded.

ii) Articles published before 2000 were discarded.

iii) Articles classified as reviews, systematic reviews, book chapters, studies on incorrect pathogens, journalistic content, strictly microbiological or therapeutic studies, theoretical immunology, and theoretical epidemiology were excluded (Vanderburg et al., 2014).

Only articles reporting on the epidemiology of *C. burnetii* were included. Articles in English, Spanish, Portuguese, and French were considered.

### *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. Several aspects were considered, as follows: epidemiological data reported, population studied, diagnostic tests performed, sample sources analyzed, infection behavior in humans and animals, case report analysis, therapies used to treat the disease in humans, risk factors associated with the pathogen.

### *Serological study in Colombia*

A cross-sectional study was conducted to evaluate the presence of IgG antibodies in blood samples obtained from 177 patients who sought medical care at the E.S.E Hospital Municipal de Montelíbano (Córdoba province) between September 30 and October 2, 2019.

Samples were collected, processed, and stored at the Molecular Diagnostic and Bioinformatics Laboratory (Universidad de Los Andes, Bogotá D.C., Colombia). All participants signed an informed consent form and completed a survey on epidemiological variables. Blood samples (5 mL) were collected in tubes without anticoagulant, centrifuged at 400g for 10 minutes to separate the serum, and analyzed for the presence of IgG Phase II antibodies against *C. burnetii*, associated with the acute form of Q fever.

The detection was performed using the NovaLisa kit (NovaTec Immunodiagnostica GMBH, Dietzenbach, Germany). Each sample was read at absorbance values of 450 and 655 nm and interpreted based on nephelometric turbidity units (NTU), following the manufacturer's instructions. Sera were classified as follows:

- Positive: NTU > 11
- Doubtful: 9 NTU to 11
- Negative: NTU < 9

## Results

### *Epidemiological analysis in humans*

For epidemiological studies on *Coxiella burnetii* in humans across South America, a total of 57 articles were identified, covering nine countries (Argentina, Brazil, Chile, Colombia, Ecuador, French Guiana, Peru, Uruguay, and Venezuela). These studies reported different seropositivity values (Table 1):

- Argentina: 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% to 100.00%
- Peru: 9.00%

•Uruguay: 37.00%

•Venezuela: 5.31% to 8.90%

No epidemiological reports were found for Bolivia, Guyana, Paraguay, or Suriname. This may be due to the limited number of studies focusing on this pathogen in these countries. Additionally, the variability in clinical manifestations, the presence of non-specific symptoms, and the absence of mandatory notification for this pathogen in both humans and animals in many South American countries contribute to the lack of epidemiological data (Eraso-Cadena et al., 2018).

Among the analyzed samples, serum was the most common, appearing in 85.96% (49/57) of the articles. Other sample types included blood, bronchoalveolar lavage, heart valves, computed tomography scans, and fecal samples (Supplementary Appendix). Of the studies reviewed, 77.19% (44/57) were population-based, while 22.81% (14/57) focused on case studies.

A significant difference in seropositivity was observed between populations with and without exposure to this pathogen. General community-based studies reported lower seroprevalence levels, whereas higher rates were found in farmers, soldiers, police officers, immunosuppressed patients, and rural populations. Particularly noteworthy are studies analyzing seroprevalence in patients with suspected dengue, which reported seroprevalence levels ranging from 3.30% to 21.40% (Mares-Guia et al., 2016; França et al., 2022; Meurer et al., 2022). Additionally, patients with endocarditis, acute febrile syndrome, and Pneumonia should be considered as key populations for the diagnosis of this pathogen. Finally, to investigate the association between chronic Q fever and imunosuppression, an analysis of HIV patients was conducted. This study found that out of 125 patients, 3.20% (n=4) tested positive for Phase I antibodies to *C. burnetii* (Lamas et al., 2009). Although this finding suggests a possible association between chronic Q fever and immunosuppression, the actual prevalence remains uncertain due to the limited number of studies on this topic.

**Table 1.** Comparative seropositivity percentages in humans and animals by country.

| 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*

Regarding epidemiological studies on animals, 52 articles were identified across nine countries: Argentina, Brazil, Chile, Colombia, Ecuador, French Guiana, Paraguay, Uruguay, and Venezuela. As observed in human studies, seropositivity rates varied depending on the region analyzed. These findings indicate the circulation of *C. burnetii* in South America, with infections detected in 14 different species (Figure 2).

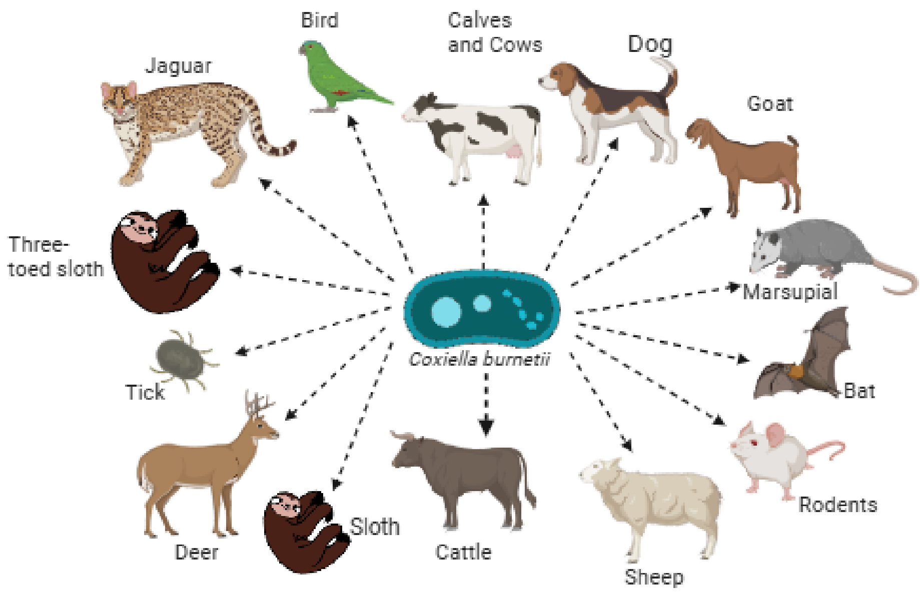


**Figure 2.** Reported *C. burnetii* infections in various animal species across South America. (Figure created using BioRender; https://biorender.com/).

In South America, *C. burnetii* infection has been detected in both wild and domestic animals, including bats, birds, cattle, cows, deer, dogs, goats, jaguars, marsupials, rodents, sheep, sloths (both two-toed and three-toed), and ticks. Among the analyzed samples, there were serum, organs, tissues, eggs, fetuses, blood, placenta, stool, bronchoalveolar lavage, vaginal and anal mucus, and larvae from small animals such as ticks (Supplementary Appendix).

It is important to note that cut-off titers for seropositivity are not well-defined in many animal species and vary between studies (Cicuttin et al., 2013). Mioni et al. (2022) quantified three positive samples in cattle, reporting *C. burnetii* concentrations ranging from $5.69 \times 10^2$ to $4.57 \times 10^4$ bacteria/mL. The presence of the pathogen in different tissues suggests a generalized bacterial distribution during infection.

### *Epidemiological analysis in food*

The seroprevalence of *C. burnetii* in food products was reported as follows: Brazil: 4.60% to 100.00%, Chile: 2.10% to 76.00%, and Colombia: 6.00% to 45.00%.

Positive *C. burnetii* DNA samples were detected in bovine, sheep, and goat milk (7 studies) and cheeses (2 studies) (Supplementary Appendix). These findings suggest a potential oral transmission route for this pathogen, which should be considered.

Rozental et al. (2020) reported that approximately 9.4% (n=5) of tested artisanal Minas cheese (MAC) samples contained *C. burnetii* genetic material. Given that Minas cheese production reaches 16.2 tons daily, this implies that up to 1.62 tons per day could be contaminated (Rozental et al., 2020).

It is important to note that a negative test result does not necessarily confirm the absence of *C. burnetii,* as detection methods for this pathogen in food products have not yet been fully standardized (Contreras et al., 2015). Additionally, the infective dose for oral transmission remains undetermined, though recent studies suggest it may be higher than the inhalation dose (1-10 bacteria) (Zanatto et al., 2019b).

### *Clinical manifestations in humans*

Most *C. burnetii* infections are self-limiting, but in some cases, they can progress to acute or chronic phases. Approximately 40% of infected individuals develop acute Q fever, which presents in three primary forms: Flu-like syndrome, hepatitis, and Pneumonia (Rozental et al., 2012; Orrego et al., 2020). Pneumonia is the most common acute presentation. In French Guiana, *C. burnetii* has been implicated in 24% of community-acquired pneumonia cases (Edouard et al., 2014).

Other symptoms of acute Q fever may include: myalgia, encephalitis, aseptic meningitis, headache, anorexia, prolonged high fever, asthenia, dry cough, respiratory distress, general malaise, pleuritic chest pain, rash, pericarditis, myocarditis, and radiographic pulmonary infiltrates (Rozental et al., 2012; Echeverría et al., 2019; Von Ranke et al., 2019).

Deaths are rare and usually occur in immunosuppressed patients or in cases involving highly virulent strains. In French Guiana, the MST17 strain (genotype 17), associated with the QpH1 plasmid, has been identified as one of the most pathogenic *C. burnetii* strains worldwide, with a strong tropism for lung tissue (Mahamat et al., 2013; des Vaux et al., 2024).

In contrast, chronic Q fever occurs in less than 5% of cases, with some estimates as low as 2% (Echeverría et al., 2019; Orrego et al., 2020). This chronic form results from persistent infection, which may manifest months or even years after the acute phase, often making it difficult for patients to recall the initial exposure, thus complicating diagnosis (Echeverría et al., 2019; Von Ranke et al., 2019).

Endocarditis is the most common chronic manifestation, accounting for 60-70% of chronic Q fever cases (Cornejo et al., 2020). It is frequently associated with pre-existing conditions such as valve disease or immunosuppression (Rozental et al., 2012). Other possible chronic manifestations include: vascular infections, prosthetic arthritis, persistent fatigue, lymphadenitis, granulomatous lesions in bones, lungs, liver, joints, testes, and soft tissues (Rozental et al., 2012; Echeverría et al., 2019; Orrego et al., 2020).

Pulmonary involvement, though primarily linked to the acute phase, has been reported in some chronic Q fever cases, often accompanied by intense headaches, myalgia, and joint pain (Rozental et al., 2012).

### *Clinical manifestations in animals*

Although *C. burnetii* infection is often subclinical in animals, one of the most common manifestations is spontaneous abortion. This is due to the bacterium's tropism for the uterus, mammary glands, and placenta (Oropeza et al., 2010). Abortion associated with *C. burnetii* has been documented in dogs, cats, sheep, cows, and goats (highly susceptible species) (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 studies have linked *C. burnetii* infection to premature death of infected animals, endometritis, mastitis, and infertility (Cicuttin et al., 2013; Zanatto et al., 2019a).

Other researchers have even suggested an association between *C. burnetii* infection and infectious bovine rhinotracheitis, viral diarrhea, and anorexia in cattle (Macías-Rioseco et al., 2019).

***Case reports***

To explore how these symptoms and diseases are presented, an analysis of the individual cases recorded was carried out. For human patients with pneumonia, five case report articles were found (Meza & Rosso, 2012; Baret et al., 2000; 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., 2000; Rozental et al., 2012). The majority of cases had ill-defined opacities on chest radiographs and increased bilateral pulmonary infiltrates. Diffuse skin lesions were observed in one case (Meza & Rosso, 2012). Laboratory findings included 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). Additionally, Baret et al. (2000) conducted an analysis comparing patients with pneumonia due to *C. burnetii* with pneumonia caused by another agent. They found that pneumonia due to *C. burnetii* generally presents with greater severity, with chills, sweating, headache, joint pain, and high levels of C-reactive protein in the blood. On the other hand, symptoms and signs such as body temperature greater than 38.5°C, respiratory symptoms, radiographic signs, lymphocyte counts, platelet counts, 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 human patients with endocarditis were recorded. These patients were characterized by 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; Lamas et al., 2013; Mahamat et al., 2013; Mizuta et al., 2022).

Finally, four articles detailed case reports in which patients did not present an association with 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 presented a rash (de Lemos et al., 2018; Uribe et al., 2021). Laboratory tests showed pulmonary involvement, such as edema and altered 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 have been recorded, mainly based on ciprofloxacin, cephalosporins, gentamicin, vancomycin, chloroquine, amoxicillin, clavulanic acid, azithromycin, meropenem, levofloxacin, rifaprim, and amphotericin (Baret et al., 2000; Siciliano et al., 2008; Lemos et al., 2011). Nevertheless, since *C. burnetii* has shown resistance to commonly used empirical antibiotics, especially for the treatment of endocarditis with negative blood cultures, such as β-lactams and aminoglycosides, when this pathogen is suspected, treatment should be initiated mainly with doxycycline (Mattar and Parra, 2006). This therapy can be administered as monotherapy, only with doxycycline (Baret et al., 2000), or in combination with other antibiotics such as doxycycline+chloroquine, doxycycline + levofloxacin, and doxycycline+ciprofloxacin (Siciliano et al., 2008).

According to Siciliano et al. (2008), the doxycycline+chloroquine treatment has been established as the shortest and most effective therapy for severe manifestations (18 months). However, constant monitoring is required due to its ocular toxicity. If chloroquine is not available, ciprofloxacin can be used, but with an extended treatment duration of up to 72 months. Furthermore, doxycycline+fluoroquinolone (levofloxacin-namacrol) has been proposed as an alternative treatment, although it may require therapies lasting up to four years.

Finally, monotherapy with macrolides has also been reported, showing an initial response. However, discontinuation is associated with a high risk of recurrence (Siciliano et al., 2008). Therefore, since *C. burnetii* is resistant to β-lactams and aminoglycosides, most articles recommend targeted therapy with antibiotics that have demonstrated efficacy, such as rifampicin, tetracyclines, and fluoroquinolones. Doxycycline remains the best alternative, typically administered in two doses of 100 mg per day for a duration ranging from 14 days to 18 months, depending on the patient's clinical manifestations (Baret et al., 2000). For individuals intolerant to doxycycline, macrolide or fluoroquinolone therapy has been proposed as an alternative.

***Diagnosis techniques***

The methods that allow the direct detection of this microorganism, such as cell culture and polymerase chain reaction (PCR), are considered the most appropriate diagnostic techniques. However, in South America, specialized laboratories equipped to perform these tests are not always available. Cell culture, in particular, is a high-risk, expensive, and complex procedure for *C. burnetii* due to the difficulty of isolating this microorganism in cell lines. For this reason, serological alternatives are more frequently used. In South America, serology was the most commonly used technique in studies conducted in humans and animals (64.91% and 40.38%, respectively) (Figure 3).

Serological analyses are characterized by their simplicity and rapidity, allowing researchers to distinguish between primary and secondary infections and to estimate the disease phase based on the immunoglobulin isotype and antigen analyzed. However, these tests are 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 minimize these limitations, many articles combined serological techniques with molecular methods. Unlike studies in humans and animals, in food-related studies, PCR and its variants were the most frequently employed diagnostic techniques (100%) (Figure 3).

A study by França DA et al. (2023) compared three serological methods for detecting *C. burnetii* antibodies: commercial IFA, in-house IFA, and ELISA. The results demonstrated good agreement between the commercial and in-house IFAs, while ELISA showed high specificity but low sensitivity. As the use of whole antigens in serodiagnosis can lead to cross-reactivity with other closely related proteobacteria, Fontes et al. (2021) demonstrated that certain Coxiella-like bacteria belonging to clades A and C yielded positive PCR results when tested with primers initially believed to be specific for *C. burnetii*. This finding underscores the need for further research and standardized techniques to accurately differentiate these pathogens. Additionally, variations in seropositivity cut-offs between studies may influence disease diagnosis.

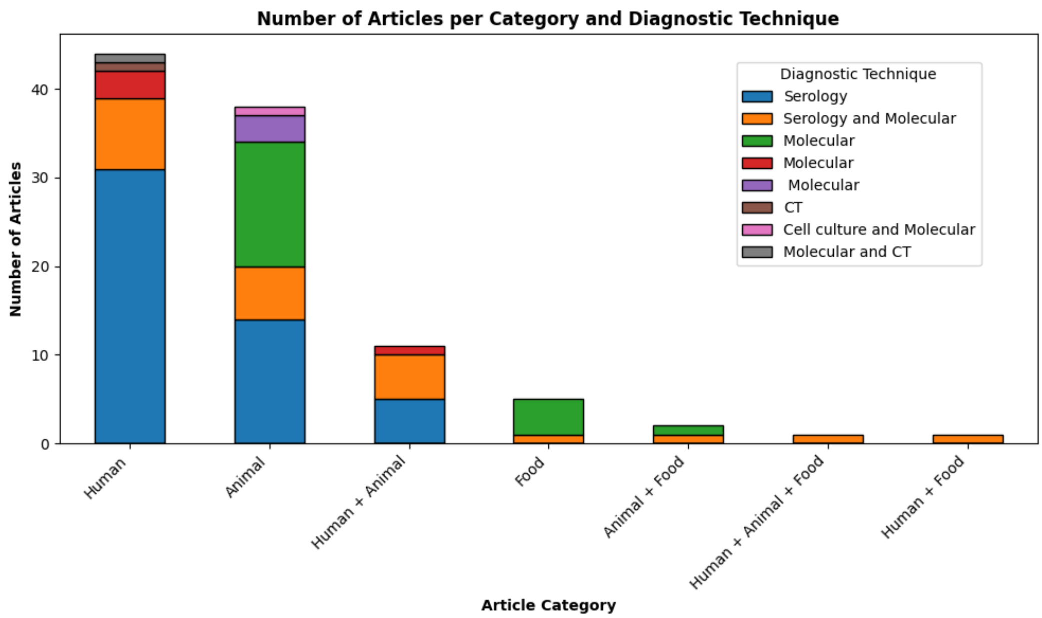


**Figure 3.** Diagnostic techniques used across studies.

Finally, since many of the studies associated with acute Q fever identified the presence of visible infiltrates on chest radiographs as a diagnostic approach, Von Ranke et al. (2019) analyzed the main patterns observed in high-resolution computed tomography (HRCT). According to this study, the main patterns include ill-defined opacities on the chest radiograph, with consolidations and nodules displaying halos of opacity appearing in later stages of the disease. In its early stages, radiographic findings may be unremarkable. Nevertheless, although these irregular contours and halos of opacity are observed, pneumonia caused by Q fever cannot be differentiated from pneumonia caused by other agents based on radiographic findings alone.

### *Risk factors*

Among the possible risk factors, occupational exposure ranks first. Individuals with a high frequency of close contact with animals and their by-products, such as veterinarians, farmers, and slaughterhouse workers, are particularly at risk (Mattar et al., 2014; De Lemos et al., 2018). Likewise, studies conducted on patients positive for Q fever in South America showed that seropositivity is higher in young adults, immunosuppressed patients, and individuals with a history of tick bites, cattle slaughter, prolonged exposure to cattle, or cohabitation 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 between exposure to feces and an increased risk of transmission of *C. burnetii* via aerosols. In addition, Gardon et al. (2001) proposed other relevant risk factors, including residing near forests, frequent sightings of wild mammals, and traveling in air-conditioned vehicles.

Regarding risk factors associated with animal infections, studies on goats identified intensive farming as a relevant factor; in sheep, male sex and geographic location were associated with higher prevalence (de Souza et al., 2018), and in cattle, infection was more frequent in females and individuals older than four years (Carbonero et al., 2015). Regarding the relationship between abortion and *C. burnetii* seropositivity, Changoluisa et al. (2019) found no significant association. As for risk factors for food contamination, these remain unclear. For instance, Betancur-Jiménez et al. (2015) reported no significant association between seropositivity and the consumption of raw milk or contact with birth products, while Siciliano et al. (2006) concluded that milk consumption is not considered a potential risk factor.

***Seropositivity in patients from a Colombian rural area***

Of the 177 blood samples analyzed, collected in 2019 at the Hospital of Montelíbano (Córdoba, Colombia), all participants signed informed consent approving the use of their samples (Ethics Committee of the Universidad de los Andes, Bogotá D.C., Colombia). Of these participants, 71.2% were women, the majority belonged to a mixed-race population (73.4%), and 61% reported contact with animals. Among the samples, eight were positive for Phase II IgG antibodies (associated with the acute manifestation of Q fever) against *C. burnetii*, representing a seropositivity rate of 4.5% (Table 2). Notably, seven of the eight seropositive individuals were women, and 75% had a history of contact with rodents in and around their homes. Additionally, 62.5% reported contact with animals.

This could indicate a relevant role of rodents in the transmission of the bacteria to humans and suggest that women may be more exposed to infection by this agent. However, further studies are needed to characterize the epidemiological patterns of the infection in Colombia. Finally, it is noteworthy that one of the patients who tested positive for *C. burnetii* IgG antibodies had also previously tested positive for arenavirus IgG antibodies. Although this does not confirm coinfection, as an active infection was not being analyzed, it highlights the need for further epidemiological investigations.

**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 | – |
| *Presence of ectoparasites* | Yes | 39 | 22 | – |
| | 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 | – |
| *Occupation* | Housekeeper | 61 | 34.5 | – |
| | Farmer | 12 | 6.8 | – |
| | Student | 16 | 9.0 | – |
| | Health care field | 14 | 7.9 | – |
| | Others | 54 | 30.5 | – |
| | NA | 20 | 11.3 | – |

NA: Not applicable

## Discussion

The reviewed studies confirm 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. Notably, the percentage of seropositivity or seroprevalence varied depending on the country studied and whether the studies were conducted in humans or animals. Brazil and French Guiana reported the highest levels of seropositivity in both humans and animals, which may be related to 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 epidemiological data were available for these regions.

Regarding the diversity of animals documented with *C. burnetii* infection in South America, studies indicate a high diversity of susceptible hosts (Figure 2). Ruminants are the main reservoir, but the role of ticks and bats in the region cannot be overlooked, as they may facilitate the widespread and rapid transmission of the bacterium to humans (Almeida et al., 2012; Ferreira et al., 2018). Currently, more than 40 species of ticks have been identified as potential carriers of *C. burnetii*, demonstrating the role these vectors may play in spreading the infection to wild and domestic vertebrates. Additionally, rodents merit special attention, as they could serve as transmission vectors to humans (Machado-Ferreira et al., 2016; de Oliveira et al., 2018). Similarly, *C. burnetii* infection in bats (order *Chiroptera*) also requires further investigation. These animals are distributed across all continents except Antarctica and exhibit a high degree of interaction with humans and other animals due to their colonial behavior, which involves grouping large numbers of reproductive individuals (Ferreira et al., 2018).

Regarding the presence of *C. burnetii* in food products, studies have confirmed its detection in milk and cheese (including artisanal cheese from Minas, Brazil), underscoring the need for constant surveillance of these products. Although it has been documented that the main source of *C. burnetii* transmission to humans is through aerosols or contaminated particulate material, epidemiological evidence suggests a possible link between exposure to raw dairy products and infection. This is particularly relevant in South America, where reports from Brazil indicate that nearly 30.00% of the population consumes unpasteurized milk, and illegally sold milk amounts to approximately 900 million liters per year (Rozental et al., 2020).

Infectious diseases remain among the leading causes of morbidity and mortality in South

America, and they account for a high proportion of hospital emergency and outpatient visits (Mahamat et al., 2013). The lack of awareness and diagnosis of *C. burnetii* infections only exacerbates this situation. This bacterium presents a particular challenge because its symptoms are often confused with those of other infectious agents commonly circulating in the region, such as dengue and chikungunya. Consequently, diseases like Q fever remain undiagnosed, worsening the problem (Rozental et al., 2012; Eraso-Cadena et al., 2018). Different areas of South America are considered endemic regions for dengue, spotted fever group (SFG) rickettsioses, chikungunya, and Zika. These diseases exhibit overlapping symptoms with Q fever, and laboratory tests for *C. burnetii* are rarely performed (Mares-Guia et al., 2016).

Q fever is asymptomatic in most cases, but it can present in both chronic and acute phases. The acute phase is the most frequently reported in South America, while the chronic manifestation is mainly linked to persistent infection or immunosuppression in affected individuals. The acute phase typically progresses in one of three forms: flu-like syndrome, hepatitis, or pneumonia. However, in South America, pneumonia has been the most frequently associated clinical presentation, often accompanied by symptoms such as fever, chills, abdominal pain, fatigue, respiratory compromise, and muscle weakness.

In contrast, the chronic phase of Q fever most commonly presents as endocarditis, with associated 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), hematuria, and decreased urine output. Laboratory findings have also revealed retinal hemorrhage, anemia, proteinuria, low complement levels, pulmonary edema, and aortic insufficiency in affected individuals. Although these findings may vary depending on the individual's underlying health conditions and age, it is crucial to identify the most common clinical indicators of Q fever. For example, Baret et al. (2000) established that *C. burnetii* pneumonia tends to be more severe than other types, frequently presenting with chills, sweating, headache, joint pain, and high levels of C-reactive protein in the blood. Moreover, laboratory studies should be complemented with epidemiological surveys to assess prior contact with cattle.

Regarding *C. burnetii* infections in animals, reported clinical manifestations include abortions, premature deaths, endometritis, mastitis, infertility, infectious rhinotracheitis, viral diarrhea, and anorexia in cows. These outcomes translate into significant economic losses, highlighting the need for further research on the circulation of this pathogen. Doxycycline remains the first-line treatment in most cases; however, to shorten therapy duration, it may be combined with other antibiotics such as chloroquine or hydroxychloroquine.

The most frequently used diagnostic techniques in the analyzed studies were serological tests due to their speed and ease of application. Serology is particularly valuable because it enables the differentiation between active or recent infections and allows for the monitoring of recurrent infections by detecting fourfold increases in IgG titers (Rozental et al., 2012). However, due to potential cross-reactivity with other bacteria, including *Bartonella, Rickettsia*, and *Legionella*, it is recommended to complement serological analyses with molecular techniques, preferably PCR. For acute Q fever, PCR testing is most effective during the first two weeks after symptom onset and should ideally be performed before antibiotic administration. If antibody-based detection is used, testing should be conducted after the third week of symptom onset, as most individuals convert during this period (Baret et al., 2000; Lamas et al., 2013).

Based on the available data, the primary risk factors for Q fever in humans include contact with animals, prolonged exposure to cattle, slaughterhouse work, fecal exposure, tick bites, immunosuppression, young adulthood, occupational exposure, and even living in air-conditioned environments, which may facilitate pathogen transmission. In animals, the proposed risk factors include intensive farming, male sex (in sheep), and advanced age (in cattle), with female cattle exhibiting higher seropositivity rates. However, since many of the studies lacked random sampling, risk factor analyses may be biased toward specific populations.

In Colombia, ELISA testing conducted in Montelíbano (Córdoba) revealed a seropositivity rate of 4.5%. This is comparable to findings from Molina-Guzmán et al. (2019), who reported a 2.3% seropositivity rate among cattle farmers in San Pedro de los Milagros (Antioquia). These results suggest that *C. burnetii* is present in Colombia, particularly in the Caribbean region, where close contact with livestock is common. Previous studies, such as Mattar and Parra (2006), reported even higher seropositivity rates (23.6%) in individuals from Córdoba and Sucre, reinforcing concerns about ongoing pathogen circulation.

In conclusion, *Coxiella burnetii* is an underestimated yet significant public health concern in South America. Epidemiological reports suggest varying seroprevalence levels across the region and between human and animal populations. The infection not only affects human health but also impacts animal welfare and causes economic losses. Therefore, it is crucial to include Q fever in differential diagnoses for infectious diseases in the region. More epidemiological studies and surveillance efforts are needed to assess the transmission dynamics, prevalence, and risks associated with this pathogen.

## Declarations

### *Acknowledgements*

Thanks to Professor Maria del Pilar Delgado (Universidad de los Andes) for her support during the experiments.

### *Conflict of interest*

The authors declare that they have no conflict of interest.

### *Funding*

This study was funded by Universidad de los Andes (Bogotá D.C., Colombia), Universidad El Bosque (Bogotá D.C-, Colombia), and Universidad Nacional, sede Medellín (Colombia). No specific grants were received from funding agencies in the public, commercial, or not-for-profit sectors.

### *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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