Caseous lymphadenitis in small ruminants. A review

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ABSTRACT
Objective: The main articles published on *Caseous lymphadenitis* (CL) in small ruminants were analyzed, consulting Google Academic, Scopus, and PubMED web pages available on the Internet.
Results: CL infection is an endemic disease, mainly in the herds of Mexico. There are strategies to prevent CL, although vaccines are not widely efficient. The clinical signs are evident, and CL can be prevented.
Study Limitations/Implications: Few studies in Latin America have described the etiology, diagnosis, and prevention of CL.
Findings/Conclusions: CL is a common disease in sheep and goat flocks. The disease affects the productivity of animals. However, there are good strategies for diagnosis, treatment and prevention.

Keywords: *Caseous lymphadenitis*; small ruminants; diagnosis; control; prevention.

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INTRODUCTION

Caseous lymphadenitis (CL) is a chronic infectious disease characterized by abscess formation and two clinical manifestations: visceral (subclinical) and cutaneous (clinical). The etiological agent, *Corynebacterium pseudotuberculosis*, is widely distributed in sheep and goat production areas, leading to significant economic losses (Szwako & Ortíz, 2014). In Canada, 36% of goat carcasses were found to have abscesses caused by *C. pseudotuberculosis*, which was associated with a substantial increase in carcass trimming and confiscation (Arsenault *et al.*, 2003). CL negatively impacts animal health and productivity, leading to systemic deterioration, reproductive disorders, mastitis, skin lesions, reduced carcass quality, and mortality (Alves *et al.*, 2018; Araujo *et al.*, 2020). The incidence of CL increases with age, with morbidity rates reaching up to 40% of the herd and mortality rates up to 4% in goat populations (Debien *et al.*, 2013). CL is characterized by the formation of abscesses

within the subcutaneous lymphatic system and the abdominal and thoracic cavities. The causative bacterium is a facultative intracellular pathogen that induces granulomatous hypersensitivity reactions (Delgado *et al.*, 2015). CL presents as a chronic pyogenic infectious disease with two forms: clinical, characterized by hypertrophy and abscesses of superficial lymph nodes, and subclinical, affecting internal organs and/or lymph nodes within the abdominal and thoracic cavities (Barnabé *et al.*, 2019). External CL lesions initially manifest as abscesses that later develop into pyogranulomas, predominantly within the superficial lymph nodes. Hair loss over affected areas occurs due to the dermonecrotic action of *C. pseudotuberculosis* exotoxins, while atrophy results from pressure exerted by the overlying skin. Visceral CL lesions are not clinically detectable but contribute to progressive weight loss, respiratory disorders, and ruminal tympany (Oreiby, 2014). The presence of one or more superficial swellings anatomically linked to lymph nodes strongly suggests CL and requires laboratory confirmation. Identification of *C. pseudotuberculosis* is achieved through bacterial culture of isolates obtained from lesions (Bastos *et al.*, 2011). For bacteriological diagnosis, lesion contents must be aseptically collected after thorough disinfection of the granuloma with an antiseptic solution. Proper disinfection prior to sampling is critical, as contamination with saprophytic bacteria may obscure *C. pseudotuberculosis* growth in culture media (Oreiby, 2014; Harwood & Mueller, 2018). The eradication of CL remains challenging due to the rapid transmission of the disease once introduced into a herd (Oreiby *et al.*, 2013). This review aims to provide an updated overview of *Corynebacterium pseudotuberculosis*, including its pathogenesis, diagnosis, control, prevention, and treatment in sheep and goats. To achieve this, an extensive literature search was conducted to compile recent findings on *Caseous lymphadenitis* in small ruminants.

Etiology

Corynebacterium belongs to the suborder *Corynebacterineae*, which includes the families *Corynebacteriaceae*, *Mycobacteriaceae*, and *Nocardiaceae*. This group shares common characteristics, including a cell wall primarily composed of peptidoglycan, arabinogalactan, and mycolic acids, as well as a high guanine-cytosine (G+C) content in the genome (Bastos *et al.*, 2012; Parise *et al.*, 2021). *Corynebacterium pseudotuberculosis* is a pleomorphic, Gram-positive bacterium that is facultative anaerobic and intracellular, with a size ranging from 0.5 to 0.6 μm (Díaz *et al.*, 2014; De Oliveira *et al.*, 2018). This bacterium infects both animals and humans, causing chronic diseases such as mastitis, *caseous lymphadenitis* in small ruminants, ulcerative lymphangitis in horses, and necrotizing lymphangitis in humans (Shi *et al.*, 2019). *C. pseudotuberculosis* strains are classified into two biovars. Strains capable of nitrate reduction belong to biovar equi, predominantly isolated from horses and cattle, while strains that do not perform nitrate reduction are classified as biovar ovis, frequently found in sheep and goats (Araujo *et al.*, 2016; Auad *et al.*, 2017). The genetic determinants of *C. pseudotuberculosis* virulence remain poorly characterized. A total of 19 identified proteins and approximately 1,230 genomic sequences have been studied, most of which are associated with virulence factors or act as positive modulators of genes encoding pathogenic virulence factors (D'Afonseca *et al.*, 2008). Among the most significant genes is PLD, which encodes an exotoxin likely involved in bacterial dissemination. The *FagA*,

FagB, *FagC*, and *FagD* genes facilitate iron acquisition, a critical factor for bacterial survival within the host. Heat shock proteins (HSPs) are known to elicit humoral and cellular immune responses, granting them immunogenic properties. The RecA protein plays a role in homologous recombination and DNA repair, while the rpoB gene encodes the β subunit of DNA-dependent RNA polymerase. Notably, evidence suggests that rpoB is also associated with rifampin resistance (D'Afonseca *et al.*, 2008; Galvão *et al.*, 2017; Marques da Silva *et al.*, 2021; Meng *et al.*, 2023).

Epidemiology

Corynebacterium pseudotuberculosis is a microorganism that is difficult to control due to its poor response to treatment, persistence in the environment, and the limited availability of diagnostic tests to detect subclinically infected animals (Abebe & Sisay, 2015). The incubation period ranges from 2 to 8 months, with detection typically occurring only when abscesses become visible in the superficial lymph nodes (Firdaus *et al.*, 2017; Harwood & Mueller, 2018). However, the epidemiology of CL varies across different animal production systems, with higher incidence rates reported in regions practicing intensive farming (Abebe & Sisay, 2015). In Brazil, prevalence rates of 93.88% have been reported in sheep, while goats showed a prevalence of 87.8% (De Farias *et al.*, 2019; Alves *et al.*, 2020b). In Egypt, prevalence in sheep was recorded at 83.65% (Selim *et al.*, 2021). In goats in Italy, a prevalence of 49.34% was reported (Bettini *et al.*, 2022). In Mexico, a prevalence of 33% was found in sheep and goats in Jalisco (Hernández *et al.*, 2019). Several risk factors contribute to high disease prevalence, including purebred status, lack of segregation by sex or age, failure to treat abscesses before spontaneous rupture, and delayed culling of seropositive animals (De Farias *et al.*, 2019; Alves *et al.*, 2020a; Alves *et al.*, 2020b). Surface lipids, known as mycolic acids, confer resistance to the bacterium by preventing drug penetration (Sá *et al.*, 2018). This microorganism can survive in the environment for extended periods: up to 8 months in soil within pus, 4 months in contaminated pens, and 2 months in straw, hay, and fomites. Low temperatures and high humidity further prolong its survival (Zeru & Kahsay, 2014; Constable *et al.*, 2017).

CL presents in two distinct forms: (A) The superficial form, characterized by abscesses in the superficial lymph nodes and subcutaneous tissue, with the mandibular (36.8%) and parotid (31.5%) lymph nodes being the most affected (Chikhaoui *et al.*, 2014). (B) The visceral form, involving abscesses in internal organs, particularly the lungs, liver, kidneys, mediastinal lymph nodes, and other lymphatic tissues (Figure 1) (Izgür *et al.*, 2010; Singh *et al.*, 2016).

Lesions caused by CL contribute to chronic weakness in affected animals (Gururaj *et al.*, 2018). The visceral form is less common in goats than in sheep (Oreiby *et al.*, 2013), and goats with internal abscesses do not always exhibit enlarged peripheral lymph nodes (Habuš *et al.*, 2015; Matthews, 2016).

Transmission

Infection can occur through direct contact with pus, consumption of contaminated water or food, and inhalation of aerosols or contaminated materials (Constable *et al.*,

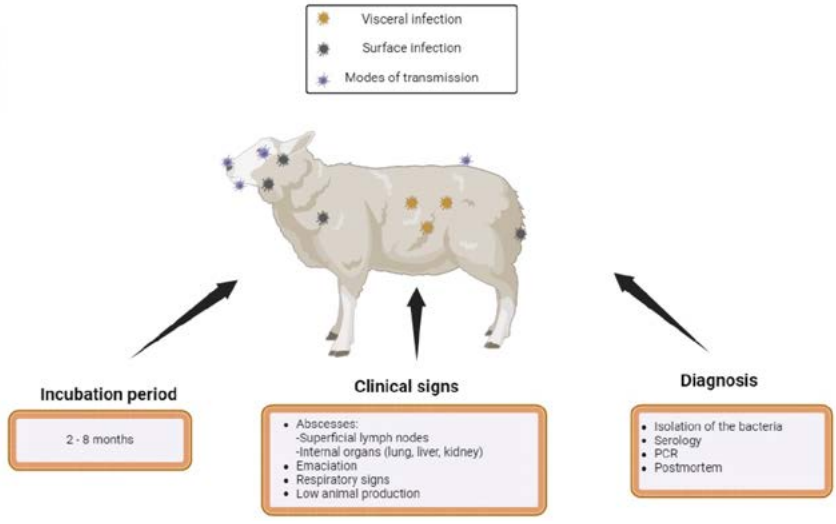

Figure 1. Most affected anatomic regions by *caseous lymphadenitis* in small ruminants.

2017; Barnabé *et al.*, 2019; De Oliveira *et al.*, 2021). Transmission between animals typically results from the contamination of superficial wounds caused by shearing, castration, vaccination, and tethering (Habuš *et al.*, 2015; Quiroga *et al.*, 2019; De Oliveira *et al.*, 2021). Vectors such as *Musca domestica* and *Hippobosca equina* have been implicated in the transmission of *C. pseudotuberculosis*, as documented in the United States, Israel, and Egypt (Costa *et al.*, 2013; Viana *et al.*, 2017). Another possible route of transmission is through mucosal contact (Harwood & Mueller, 2018). The bacteria can colonize the tonsils following ingestion, with young animals becoming infected by consuming contaminated milk directly from the mother's udder (Matthews, 2016). Spontaneous rupture and drainage of abscesses facilitate the environmental dissemination of *C. pseudotuberculosis*, increasing the risk of transmission (Rezende *et al.*, 2016). Once discharged from an abscess, the bacteria can persist in the environment, as well as in hay, soil, and manure (Matthews, 2016; Schlicher *et al.*, 2021). The spread of the pathogen between farms commonly occurs through the introduction of infected animals, contaminated equipment, and shared livestock facilities (Matthews, 2016).

Pathogeny and Immune Response

All *Corynebacterium pseudotuberculosis* strains produce an exotoxin known as phospholipase D (PLD), which is a key virulence factor responsible for pathogen dissemination from the initial infection site within the host (Jeber *et al.*, 2016; De Oliveira *et al.*, 2018). This toxin hydrolyzes phosphatidylcholine and sphingomyelin in mammalian cell membranes, facilitating bacterial spread and causing endothelial cell necrosis. It promotes bacterial translocation from the dermis into the bloodstream and lymphatic vessels (Baird & Malone, 2010). Additionally, PLD activates the complement system, leading to necrosis and thrombosis of the lymphatic vessels (Bastos *et al.*, 2012; Barros *et al.*, 2021). The disease begins with a primary infection at a lymphatic wound, which then spreads hematogenously. Following infection, neutrophils and macrophages are rapidly

activated, initiating signaling pathways that trigger an adaptive immune response against the pathogen (Sá *et al.*, 2018). The cellular adaptive response involves CD4+ T cells, which produce Th1-type cytokines, including interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), to control infection. Proinflammatory cytokines enhance macrophage bactericidal activity and activate CD8+ T lymphocytes, which attempt to eliminate *C. pseudotuberculosis* (De Souza *et al.*, 2014; Fu *et al.*, 2020). Macrophage activation follows two pathways: classical activation (M1 macrophages), mediated by MHC class II, Toll-like receptors (TLRs), and IFN-γ, which promotes the Th1 response and enhances phagocytosis; and alternative activation (M2 macrophages), induced by IL-4, IL-13, and IL-1, which secrete anti-inflammatory molecules such as TGF-β, thereby promoting a Th2 immune response (Sá *et al.*, 2018). To evade the immune system, *C. pseudotuberculosis* can be phagocytosed by neutrophils and macrophages, forming a phagolysosome. However, PLD interferes with opsonization, allowing the bacteria to escape neutrophil and macrophage activity. It also forms a lipid layer, shielding it from proteolytic enzymes within phagolysosomes, while inhibiting macrophage nitric oxide production. These mechanisms enable the bacterium to persist intracellularly, evade immune destruction, and disseminate throughout the host (Bastos *et al.*, 2012; Jeber *et al.*, 2016; De Oliveira *et al.*, 2018; Rebouças *et al.*, 2020; Umer *et al.*, 2020; Barros *et al.*, 2021; Marques da Silva *et al.*, 2021). The humoral immune response occurs 6 to 11 days post-infection, during which antibody production helps prevent bacterial dissemination. Cytokines such as TNF-α, IL-1β, and IL-6 are primarily produced at the inoculation site by macrophages, while IL-2, IL-4, and IFN-γ are produced in the lymph nodes, contributing to T-cell activation (Guimarães *et al.*, 2011a; Bastos *et al.*, 2012; Barral *et al.*, 2022a). Uncontrolled bacterial growth within macrophages induces inflammatory cell death, leading to the formation of pyogranulomas with a caseous necrotic center one of the hallmarks of the disease. Prolonged stimulation of TLRs promotes the formation of multinucleated giant cells, which respond to cellular damage. Simultaneously, M2 macrophages attract fibroblasts, stimulating collagen deposition and forming a capsule around the lesion. As a result, these granulomatous lesions consist of a core of infected macrophages and giant cells, surrounded by T cells, B cells, neutrophils, epithelioid macrophages, and fibrous tissue. However, some bacteria remain viable within abscesses for years, leading to latent infections (Bastos *et al.*, 2012; Tizard, 2018). When an internal abscess ruptures, pus containing millions of bacteria is released, facilitating hematogenous spread to multiple organs (Barnabé *et al.*, 2019).

Granuloma formation acts as a host defense mechanism, restricting bacterial dissemination to vital organs while promoting an effective immune response (Al-Gaabary *et al.*, 2010; Bastos *et al.*, 2012). However, abscess formation provides *C. pseudotuberculosis* with immune protection, limiting antimicrobial effectiveness and enabling immune evasion (Habuš *et al.*, 2015). The pyogranuloma undergoes continuous transformation through cytokine secretion by immune cells. A chronic inflammatory reaction is sustained at the lesion center, while tissue repair processes are initiated at the periphery. This response is driven by cytokines such as IFN-γ, TNF-α, IL-4, IL-1, and IL-6 (Lefevre *et al.*, 2010; Bastos *et al.*, 2012).

Clinical Signs

This disease is characterized by the formation of abscesses in the lymph nodes and internal organs of small ruminants. However, in sheep and goats, CL does not typically cause obvious clinical signs unless the lesions are progressive, excessively large, or numerous enough to be detected clinically, or if they impair the function of a vital organ (Jeber *et al.*, 2016). The most common clinical manifestation is the presence of abscesses in the superficial lymph nodes, with the parotid, submandibular, prescapular, femoral, popliteal, and supramammary nodes being the most frequently affected (Firdaus *et al.*, 2017). Goats and sheep with internal abscesses may exhibit signs of emaciation, while involvement of thoracic lymph nodes can lead to respiratory symptoms (Matthews, 2016; Firdaus *et al.*, 2017). The incidence of CL has been shown to increase with age, with animals between 2 and 3 years being the most affected (Selim *et al.*, 2021; Bettini *et al.*, 2022).

Differential Diagnoses

When evaluating lymph node abscesses, other potential etiologies should be considered, including tuberculosis infections and bacterial abscesses caused by *Actinomyces pyogenes* or *Trueperella pyogenes* (Abebe & Sisay, 2015; Harwood & Mueller, 2018; Gascoigne *et al.*, 2020). *Staphylococcus aureus* subspecies *anaerobius* produces abscesses similar to those seen in CL, a condition known as Morel's disease, which primarily affects young animals. This disease has an incubation period of approximately three weeks, and its lesions are not always located near lymph nodes (Gascoigne *et al.*, 2020). *Actinobacillosis lignieresii* is a commensal organism in the oral cavity of ruminants and is occasionally isolated from abscesses around the face and neck in goats. Additionally, infections caused by *Yersinia pseudotuberculosis* and various Mycobacterium species can occasionally produce lesions resembling those of *C. pseudotuberculosis* (Matthews, 2016). The superficial form of CL must be distinguished from conditions such as submandibular edema caused by *Fasciola hepatica* and *Haemonchus* spp., salivary cysts, lymphosarcoma, and abscesses resulting from vaccine inoculation (Guimarães *et al.*, 2011a). The visceral form may present clinical similarities to chronic parasitism, alveolar periodontitis, malnutrition, chronic systemic diseases, pulmonary adenomatosis, neoplasms, small ruminant lentivirus infections, paratuberculosis, and scrapie (Lefevre *et al.*, 2010; Guimarães *et al.*, 2011b). In sheep, orchitis and epididymitis caused by *C. pseudotuberculosis* must be differentiated from lesions induced by *Brucella ovis*, *Actinobacillus seminis*, *Histophilus somni*, and *Pasteurella* spp. (Guimarães *et al.*, 2011b).

Sampling and Diagnosis

The clinical diagnosis through the detection of lymphadenomegaly is the method routinely performed by veterinarians, but it is nonspecific, and the standard diagnostic test is bacterial culture, followed by the identification of *Corynebacterium pseudotuberculosis* using biochemical tests (Nicoletti *et al.*, 2022). Bacterial isolation is performed by puncturing the abscess with 18G needles and sterile 10 mL syringes, ensuring prior trichotomy of the area. The sample is refrigerated, labeled, and sent to the laboratory. For lesions with superficial or ruptured abscesses, a deep smear can be obtained using sterile cotton swabs; samples are preserved in Stuart culture medium and refrigerated. The material for bacterial

culture is collected from the abscess and inoculated into brain heart infusion (BHI) agar with 5% sheep blood (Seyffert *et al.*, 2010; Oreiby *et al.*, 2013; Díaz *et al.*, 2015). This bacterium is a facultative anaerobe that grows optimally at 37 °C, with a pH of 7.0-7.2. Initial growth on agar surfaces appears sparse but later forms clumps or palisades, with a cream to orange coloration. Colonies are dry, opaque, and concentrically ringed. Growth in liquid media develops as a granular deposit with a surface pellicle. Hemolysis on blood agar is variable, but large hemolysis zones appear in the presence of *Rhodococcus equi*. *C. pseudotuberculosis* toxin also inhibits the action of staphylococcal β-lysin (Dorella *et al.*, 2016). Serological diagnosis includes indirect hemagglutination test, microagglutination assay, double immunodiffusion test, hemolysis inhibition test, interferon-gamma (IFN-γ) detection by ELISA, and the enzyme-linked immunosorbent assay (ELISA) using bacterial cells, toxins, culture supernatants, and secreted proteins (PLD) (Bastos *et al.*, 2012; Rezende *et al.*, 2016; Silva *et al.*, 2019). The ELISA test is highly specific but has low sensitivity, which may result in false negatives. However, repeating the test one month later in negative animals confirms the diagnosis (Matthews, 2016). Nevertheless, ELISA formats using recombinant proteins are promising due to their high specificity and significant sensitivity, as they use purified antigens (Silva *et al.*, 2019). The synergistic hemolysis inhibition (SHI) test measures antibodies against PLD and has a 98% sensitivity in goats, but its low specificity makes it an unreliable predictor of clinical disease in infected herds (Washburn *et al.*, 2013; Matthews, 2016). The quantification of IFN-γ produced by peripheral leukocytes following antigenic stimulation is an accurate diagnostic method but has low sensitivity and is expensive (Bastos *et al.*, 2012). The Multiplex Polymerase Chain Reaction (mPCR) is useful for diagnosing CL in small ruminants. This method is highly sensitive and specific, does not require primary isolation, and is employed in epidemiological surveillance and experimental studies (Quiroga *et al.*, 2019). Detection of the PLD gene serves as a diagnostic tool for CL. Recently, partial sequence analysis of the RNA polymerase (rpoB) β subunit gene has been used for identifying *Corynebacterium* species (Nabih *et al.*, 2018). Over the past decades, various molecular techniques such as conventional, real-time, and multiplex PCR, DNA-DNA hybridization, and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) have been applied to complement traditional diagnostic methods. These techniques also aid in studying the virulence profile, genetic diversity, and geographical distribution of *C. pseudotuberculosis* strains worldwide (Dorneles *et al.*, 2014; Parise *et al.*, 2018; Zamprogna *et al.*, 2021; Park *et al.*, 2022). Most visceral CL cases are diagnosed postmortem, revealing internal abscesses during slaughterhouse inspection (Abebe & Sisay, 2015). In goats, abscesses are typically creamy white or yellow, whereas in sheep, they are often green. Calcification is rare, and the characteristic "onion ring" appearance is observed in sheep but not in goats. The thick, sticky pus found in goats is attributed to enzymatic activity from phagocytic cells (Valdivia, 2015; Matthews, 2016).

Treatment

The animal scheduled for abscess debridement should be removed from the pen and relocated to a sun-exposed area. Preferably, the procedure should be performed in a

location with a cement floor, which facilitates washing and disinfection (Díaz *et al*., 2015). Surgical treatment is described in Figure 2.

Corynebacterium pseudotuberculosis is susceptible to various antibiotics in vitro; however, it is generally refractory to antibiotic therapy (Baird & Malone, 2010). This resistance is attributed to the intracellular nature of the organism during much of its pathogenesis and the presence of a thick fibrous abscess wall. Once an abscess has formed, treatment with commonly used antibiotics is ineffective (Izgür *et al*., 2010; Matthews, 2016; Bezerra *et al*., 2021).

Control and Prevention

Animals exhibiting clinical signs of CL and enlarged lymph nodes should be isolated from the herd to prevent abscess rupture and pus release (Harwood & Mueller, 2018). Rubefacient ointments, hot compresses, and poultices are therapeutic measures that promote abscess maturation for manual drainage (White, 2006; Tuemmers & Saldivia, 2015). The most effective strategy for CL control is identifying infected animals through clinical examination or serological testing. Culling infected animals has been successful in disease prevention (Chikhaoui *et al*., 2014; Harwood & Mueller, 2018). Animals should be examined every three months to detect visible abscesses. Serodiagnostic tests for *C. pseudotuberculosis* antibodies have been successfully implemented to identify asymptomatic infections. ELISA has been widely used in CL control and eradication programs due to

Figure 2. Procedure to debride an abscess. A) Incision in the distal region of the abscess with a sterile scalpel blade, previously disinfection of the area with 1% iodine solution or 70% ethanol must be carried out, B) Drain the purulent content into a plastic bag, C) The cavity is washed with hydrogen peroxide, 10% iodine or chlorhexidine, D) Moisten the gauze with a disinfectant solution and introduce the gauze into the cavity, scraping off the infected tissue, E) The cavity is washed again, F) Collect the contaminated material and discard.

its cost-effectiveness, ease of use, and suitability for routine clinical application (Silva *et al.*, 2019). Bacteriological and serological tests for *C. pseudotuberculosis* are highly specific, and any positive animal must be separated from seronegative groups. If an animal yields an uncertain result, it should be retested after one month and kept isolated until confirmation (Matthews, 2016).

In countries where vaccination is available, herd control measures significantly reduce disease prevalence, although complete eradication remains unattainable (Baird & Malone, 2010; Sobrinho *et al.*, 2018). The ineffectiveness of antibiotics against *C. pseudotuberculosis* has led to the development of various vaccines, including attenuated, inactivated, cell membrane fraction, and DNA-based vaccines (Guerrero *et al.*, 2018). Commercial vaccines against CL are currently available; however, their efficacy varies, and vaccination is recommended only for abscess-free animals (Barral *et al.*, 2022b). Most commercial vaccines for *C. pseudotuberculosis* are combined with *Clostridium* vaccines targeting *C. tetani*, *C. perfringens*, *C. septicum*, *C. novyi*, and *C. chauvoei*. These vaccines use inactivated phospholipase D (PLD) and are referred to as toxoid vaccines (Dorella *et al.*, 2006). PLD and CP40 proteins have been identified as potential vaccine targets, with PLD inducing a strong antibody response and CP40 activating cellular immunity (Barral *et al.*, 2022b). Vaccination of goats with a formalin-inactivated PLD exotoxin has been shown to prevent bacterial dissemination following experimental challenge, while antitoxin administration further inhibits bacterial spread within the host (Dorella *et al.*, 2009). Toxoid vaccines have demonstrated efficacy in reducing the number and size of CL lung abscesses and limiting bacterial spread. In Brazil, a live attenuated *C. pseudotuberculosis* strain (strain 1002) was approved for use, conferring 83% protection against CL in goats (Dorella *et al.*, 2006). Additionally, experimental immunogens are being tested to enhance safety and protection levels (Barral *et al.*, 2022b). Virulence genes of *C. pseudotuberculosis* are considered promising targets for vaccine development (D'Afonseca *et al.*, 2008). Most vaccine development studies focus on bacterial genes (DNA vaccines) or bacterial proteins (subunit vaccines). Another approach involves gene knockout-attenuated strains. A recent study developed an attenuated *C. pseudotuberculosis* strain with a *ciuA* gene knockout (a gene involved in iron citrate transport for bacterial metabolism). This vaccine successfully induced both cellular and humoral immune responses after challenge with the wild-type strain (Galvão *et al.*, 2017). Additionally, sheep vaccinated with a DNA vaccine expressing bovine CTLA-4 fused with HIg and genetically detoxified phospholipase D exhibited extracellular immune dominance. However, this genetically attenuated vaccine was only partially effective in experimental trials (Dorella *et al.*, 2006).

Zoonosis

As in small ruminants, *Corynebacterium pseudotuberculosis* can infect humans, causing necrotizing granulomatous lymphadenitis (Bastos *et al.*, 2012; Heggelund *et al.*, 2015; Tan *et al.*, 2021). CL has also been associated with pneumonia, particularly in individuals who have had contact with infected animals. It is considered an occupational zoonosis; however, human infections are rare. Most cases of human lymphadenitis have been reported in Australia, primarily affecting workers with regular exposure to infected sheep (Schlicher *et*

al., 2021). Transmission typically occurs through direct contact with the skin or wounds, although consumption of contaminated raw goat's milk and raw goat's cheese may also serve as potential routes of infection (Heggelund *et al*., 2015; Sigirci *et al*., 2019).

CONCLUSION

Caseous lymphadenitis is widely distributed worldwide, impacting small ruminant production and causing economic losses due to decreased productivity in these species. Given the significant effect of this disease on livestock production, we emphasize the importance of surgical debridement of abscesses to prevent environmental contamination and reduce the persistence of *Corynebacterium pseudotuberculosis* within the herd. However, based on the information compiled in this review, we highlight that preventive measures remain the most critical strategy for effective caseous lymphadenitis management.

REFERENCES

Abebe, D., & Sisay, T.T. (2015). Determination of *Corynebacterium pseudotuberculosis* prevalence and antimicrobial susceptibility pattern of isolates from lymph nodes of sheep and goats at an organic export abattoir, Modjo, Ethiopia. *Letters in applied microbiology 61*(5): 469-476. doi:10.1111/lam.12482

Al-Gaabary, M.H., Osman, S.A., Ahmed, M.S., & Oreiby, A.F. (2010). Abattoir survey on caseous lymphadenitis in sheep and goats in Tanta, Egypt. *Small Ruminant Research 94*(1-3): 117-124. doi:10.1016/j.smallrumres.201

Alves, J.R.A., Farias, A.E.M., Lima, G. M. de S., Limeira, C.H., Alves, F.S.F., Pinheiro, R.R., Faccioli-Martins, P.Y., Azevedo, S.S. de, & Alves, C.J. (2018). Soroprevalência da linfadenite caseosa em caprinos comercializados em feira de animais no Semiárido nordestino. *Semina: Ciências Agrárias 39*(3): 1067-1076. doi:10.5433/1679-0359.2018v39n3p1067

Alves, J. R. A., de Farias, A. E. M., Silva, J. D. D., Viana, M. P., Lima, A. M. C., Faccioli-Martins, P. Y., Pinheiro, R. R., Alves, F. S. F., de Azevedo, S. S., & Alves, C. J. (2020a). Factors associated with the seroprevalence of caseous lymphadenitis in sheep from Northeastern Brazil. *Preventive veterinary medicine* 182. doi:10.1016/j.prevetmed.2020.105098

Alves, J. R. A., de Farias, A. E. M., Dos Anjos, D. M., Lima, A. M. C., Faccioli-Martins, P. Y., de Souza, C. J. H., Pinheiro, R. R., Alves, F. S. F., de Azevedo, S. S., & Alves, C. J. (2020b). Seroepidemiological study of *Caseous lymphadenitis* in sheep from the Northeast region of Brazil using an indirect ELISA. *Tropical animal health and production 52*(4):1945-1952. doi:10.1007/s11250-020-02214-9

Araujo, C.L., Blanco, I., Souza, L., Tiwari, S., Pereira, L.C., Ghosh, P., Azevedo, V., Silva, A., Folador, A. (2020). In silico functional prediction of hypothetical proteins from the core genome of *Corynebacterium pseudotuberculosis* biovar ovis. *PeerJ* 8:e9643. doi: 10.7717/peerj.9643

Araujo, C.L., Dias, L.M., Veras, A.A., Alves, J.T., Cavalcante, A.L., Dowson, C.G., Azevedo, V., Ramos, R.T., Silva, A., & Carneiro, A.R. (2016). Whole-Genome Sequence of *Corynebacterium pseudotuberculosis* 262 Biovar equi Isolated from Cow Milk. *Genome announcements 4*(2): e00176-16. doi: 10.1128/genomeA.00176-16

Arsenault, J., Girard, C., Dubreuil, P., Daignault, D., Galarneau, J. R., Boisclair, J., Simard, C., & Bélanger, D. (2003). Prevalence of and carcass condemnation from maedi-visna, paratuberculosis and caseous lymphadenitis in culled sheep from Quebec, Canada. *Preventive veterinary medicine 59*(1-2): 67-81. doi:10.1016/s0167-5877(03)00060-6

Auad, J., Cooper, L., Cerutti, J., Marcelino, R., Neder, V.E., Calvinho, L.F. (2017). Aislamiento y caracterización de *Corynebacterium pseudotuberculosis* biotipo *ovis* en Lama glama en Córdoba, Argentina. *Methodo Investigación Aplicada a Las Ciencias Biológicas 2*(2):72-76. doi: 10.22529/me.2017.2(2)09

Baird, G.J., Malone F.E. (2010). Control of caseous lymphadenitis in six sheep flocks using clinical examination and regular ELISA testing. *Veterinary record 166*(12): 358-362.

Barnabé, N.N.C., Da Silva, J.D., Porto, V.M., Paiva, B.N., Gonçalves, A.E.L, Álvares, F.P.J., de Barros, A.B., dos Santos, S.S., de Azevedo, S., Alves, C. (2019). Characterization of caseous lymphadenitis in caprine animals slaughtered in a semi-arid region of Brazil. *Ciências Agrárias 40*(5): 1867-1878. doi: 10.5433/1679-0359.2019v40n5p1867

Barral, T.D., Rebouças, M.F., Loureiro, D., Raynal, J.T., Sousa, T.J., Moura-Costa, L.F., Azevedo, V., Meyer, R., & Portela, R.W. (2022a). Chemokine production induced by *Corynebacterium pseudotuberculosis* in a murine model. *Brazilian journal of microbiology 53*(2): 1019-1027. doi: 10.1007/s42770-022-00694-5

Barral, T.D., Kalil, M.A., Mariutti, R.B., Arni, R.K., Gismene, C., Sousa, F.S., Collares, T., Seixas, F.K., Borsuk, S., Estrela-Lima, A., Azevedo, V., Meyer, R., & Portela, R.W. (2022b). Immunoprophylactic properties of the *Corynebacterium pseudotuberculosis*-derived MBP:PLD:CP40 fusion protein. *Applied microbiology and biotechnology 106*(24): 8035-8051. doi: 10.1007/s00253-022-12279-1

Barros de Pinho, R., de Oliveira Silva, M.T., Brenner, G., Dié Alves, M.S., Azevedo, V., Dias Portela, R., & Borsuk, S. (2021). A novel approach for an immunogen against *Corynebacterium pseudotuberculosis* infection: An *Escherichia coli* bacterin expressing phospholipase *D. Microbial pathogenesis* 151: 104746. doi: 10.1016/j.micpath.2021.104746

Bastos, B.L., Dias, P.R.W., Alves, D.F., Ribeiro, D., Seyffert, N., de Paula, C.T.L., Miyoshi, A., Costa, S., Meyer, R. & Azevedo. (2012). *Corynebacterium pseudotuberculosis*: Immunological Responses in Animal Models and Zoonotic Potential. *Journal of Clinical and Cellular Immunology* S4: 1-15. doi: 10.4172/2155-9899.S4-005

Bastos, B.L., Meyer, R., Guimarães, J.E., Ayres, M.C., Guedes, M.T., Moura-Costa, L.F., de Burghgrave, U.S., Sena, L., Azevedo, V. & Portela, R.W. (2011). Haptoglobin and fibrinogen concentrations and leukocyte counts in the clinical investigation of caseous lymphadenitis in sheep. *Veterinary Clinical Pathology 40*(4): 496-503. doi: 10.1111/j.1939-165X.2011.00355.x

Bettini, A., Mancin, M., Mazzucato, M., Schanung, A., Colorio, S., & Tavella, A. (2022). A Seroepidemiological Survey of *Corynebacterium pseudotuberculosis* Infection in South Tyrol, Italy. *Pathogens (Basel, Switzerland) 11*(11): 1314. doi:10.3390/pathogens11111314

Bezerra, F.S.B., Silva, M.T.O., Rezende, A.F.S., Lopes, A.S., de Pinho, R.B., Seixas, F.K., Collares, T.V., Portela, R.W.D., Azevedo, V.A.C. & Borsuk, S. (2021). Saponin-adjuvanted recombinant vaccines containing rCP00660, rCP09720 or rCP01850 proteins against *Corynebacterium pseudotuberculosis* infection in mice. *Vaccine* 39: 2568-2574. doi: 10.1016/j.vaccine.2021.03.062

Chikhaoui, M., Fatima, B., Fadhela, S., Kada, K. & Yacine, T. (2014). Epidemiological and Histopathological Studies on *Caseous lymphadenitis* in Slaughtered Goats in Algeria. *Global Veterinaria 13*(6): 1065-1068. doi: 10.5829/idosi.gv.2014.13.06.9182

Constable, D.P., Hinchcliff, W.K., Done, H.S., Grünberg, W. (2017). Diseases of the Hemolymphatic and Immune systems: Veterinary Medicine a Textbook of the Diseases of Cattle, Horses, Sheep, Pigs, and Goats. EUA: Saunders.

Costa, T.L., Ribeiro, D., Hirata, R. Jr., Pacheco, L.G., Souza, M.C., dos Santos, L.S., dos Santos, C.S., Salah, M., Costa, M.M., Ribeiro, M.G., Selim, S.A., Azevedo, V.A. & Mattos-Guaraldi, A.L. (2013). Multiplex polymerase chain reaction to identify and determine the toxigenicity of *Corynebacterium* spp. with zoonotic potential and an overview of human and animal infections. *Memórias do Instituto Oswaldo Cruz 108*(3): 272-279. doi: 10.1590/S0074-02762013000300003

D'afonseca, V., Moraes, P.M., Dorella, F.A., Pacheco, L.G., Meyer, R., Portela, R.W., Miyoshi, A. & Azevedo, V. (2008). A description of genes of *Corynebacterium pseudotuberculosis* useful in diagnostics and vaccine applications. *Genetics and molecular research GMR 7*(1): 252-260. doi: 10.4238/vol7-1gmr438

De Farias, A. E. M., Alves, J. R. A., Alves, F. S. F., Pinheiro, R. R., Faccioli-Martins, P. Y., Lima, A. M. C., de Azevedo, S. S., & Alves, C. J. (2019). Seroepidemiological characterization and risk factors associated with seroconversion to *Corynebacterium pseudotuberculosis* in goats from Northeastern Brazil. *Tropical animal health and production, 51*(4), 745-752. doi:10.1007/s11250-018-1748-7

De Oliveira, S.M.T., Bezerra, F.S.B., de Pinho, R.B., Begnini, K.R., Seixas, F.K., Collares, T., Portela, R.D., Azevedo, V., Dellagostin, O. & Borsuk, S. (2018). Association of *Corynebacterium pseudotuberculosis* recombinant proteins rCP09720 or rCP01850 with rPLD as immunogens in caseous lymphadenitis immunoprophylaxis. *Vaccine 36*(1): 74-83. doi: 10.1016/j.vaccine.2017.11.029

De Oliveira, Z.T., Ribeiro, D., Azevedo, V.A.C., Lara, G.H.B., Motta, R.G., da Silva, R.C., Siqueira, A.K., de Nardi Júnior, G., Listoni, F.J.P., de Souza Araújo Martins, L., da Silva, A.V., Portilho, F.V.R., da Rocha Mota, A., Rodrigues, C.A., de Almeida, B.O., & Ribeiro, M.G. (2021). Bacteriological, cytological, and molecular investigation of *Corynebacterium pseudotuberculosis*, mycobacteria, and other bacteria in caseous lymphadenitis and healthy lymph nodes of slaughtered sheep. *Brazilian journal of microbiology 52*(1): 431-438. doi: 10.1007/s42770-020-00403-0

De Souza, A.P., Vale, V.L., Silva, M. daC., Araújo, I.B., Trindade, S.C., de Moura-Costa, L.F., Rodrigues, G.C., Sales, T.S., dos Santos, H.A., de Carvalho-Filho, P.C., de Oliveira-Neto, M.G., Schaer, R.E., & Meyer, R. (2014). MAPK involvement in cytokine production in response to *Corynebacterium pseudotuberculosis* infection. *BMC microbiology* 14, 230. doi: 10.1186/s12866-014-0230-6

Debien, E., Hélie, P., Buczinski, S., Lebœuf, A., Bélanger, D., & Drolet, R. (2013). Proportional mortality: A study of 152 goats submitted for necropsy from 13 goat herds in Quebec, with a special focus on caseous lymphadenitis. *Canadian Veterinary Journal 54*(6): 581-587.

Delgado, D.A., Zárraga, J., Chirino-Zárraga, C.I., & Carrero, P.L.L. (2015). Caracterización epidemiológica de la Linfadenitis caseosa en rebaños caprinos de la península de Paraguaná, Venezuela. *Revista de Medicina Veterinaria* (31): 35-45. https://doi.org/10.19052/mv.3706

Diaz, A.E., Tortora, P.J.L., Palomares, R.E.G., & Gutiérrez, H.J.L. (2015). Linfadenitis caseosa: Enfermedades de las cabras. (Primera edición). México: INIFAP.

Dorella, F.A., Pacheco, L.G., Oliveira, S.C., Miyoshi, A., & Azevedo, V. (2006). *Corynebacterium pseudotuberculosis*: microbiology, biochemical properties, pathogenesis and molecular studies of virulence. *Veterinary Research 37*(2): 201-218. doi:10.1051/vetres:2005056

Dorella, F.A., Pacheco, L.G., Seyffert, N., Portela, R.W., Meyer, R., Miyoshi, A., & Azevedo, V. (2009). Antigens of *Corynebacterium pseudotuberculosis* and prospects for vaccine development. *Expert review of vaccines 8*(2): 205-213. doi:10.1586/14760584.8.2.205

Dorneles, E. M., Santana, J. A., Ribeiro, D., Dorella, F. A., Guimarães, A. S., Moawad, M. S., Selim, S. A., Garaldi, A. L., Miyoshi, A., Ribeiro, M. G., Gouveia, A. M., Azevedo, V., Heinemann, M. B., & Lage, A. P. (2014). Evaluation of ERIC-PCR as genotyping method for *Corynebacterium pseudotuberculosis* isolates. *PloS one 9*(6): e98758. doi: 10.1371/journal.pone.0098758.

Droppa-Almeida, D., Franceschi, E., & Padilha, F. F. (2018). Immune-Informatic Analysis and Design of Peptide Vaccine From Multi-epitopes Against *Corynebacterium pseudotuberculosis*. *Bioinformatics and biology insights* 12. doi:10.1177/1177932218755337

Firdaus, A.J.F., Abba, Y., Nurul, S.R., Adamu, L., Athlimai, B.A., Teik, C.E.L., Sadiq, M.A., Hambali, I., Haron, W., & Mohammed, M.A. (2017). Clinical case of caseous lymphadenitis in a goat: case management. *Malaysian Journal of Veterinary Research 8*(1): 31-35.

Fu, M., Su, H., Su, Z., Yin, Z., Jin, J., Wang, L., Zhang, Q., & Xu, X. (2020). Transcriptome analysis of *Corynebacterium pseudotuberculosis*-infected spleen of dairy goats. *Microbial pathogenesis* 147, 104370. doi: 10.1016/j.micpath.2020.104370

Galvão, C.E., Fragoso, S.P., de Oliveira, C.E., Forner, O., Pereira, R.R.B., Soares, C.O., & Rosinha, G.M.S. (2017). Identification of new *Corynebacterium pseudotuberculosis* antigens by immunoscreening of gene expression library. *BMC microbiology 17*(1): 202. doi: 10.1186/s12866-017-1110-7

Gascoigne, E., Ogden, N., Lovatt, F., & Davies, P. (2020). Update on caseous lymphadenitis in sheep. *In Practice 42*(2): 105-114. doi:10.1136/inp.m455

Guerrero, J.A.V., de Oca Jiménez, R.M., Acosta Dibarrat, J., León, F.H., Morales-Erasto, V., & Salazar, H.G.M. (2018). Isolation and molecular characterization of *Corynebacterium pseudotuberculosis* from sheep and goats in Mexico. *Microbial Pathogenesis* 117: 304-309.

Guimarães, A., Carmo, F.B., Pauletti, R.B., Seyffert, N., Ribeiro, D., Lage, A.P., Heinemann, M.B., Miyoshi, A., Azevedo, V., Guimarães, A.M. (2011a). *Caseous Lymphadenitis*: Epidemiology, diagnosis and control. *IIOAB Journal 2*(2): 33-43.

Guimarães, A., Carmo, F.B., Heinemann, M.B., Portela, R.W., Meyer, R., Lage, A.P., Seyffert, N., Miyoshi, A., Azevedo, V., & Gouveia, A.M. (2011b). High sero-prevalence of caseous lymphadenitis identified in slaughterhouse samples as a consequence of deficiencies in sheep farm management in the state of Minas Gerais, Brazil. *BMC Veterinary Research*. 7, 68.

Gururaj, K., Singh, D.D., Pawaiya, R.V.S., Andani, D., Gangwar, N.K., & Mishra, A.K. (2018). Investigation of an outbreak of caseous lymphadenitis in goats. *Indian Journal of Small Ruminants 24*(1): 95-100. doi: 10.5958/0973-9718.2018.00008.9

Habuš, J., Matanović, K., Majetić, Z., Rukavina, T., Ćorić, A., Milas, Z., Starešina, V., Martinec, B.S., & Turk, N. (2015). Comparison of the epizootiological and clinical features of caseous lymphadenitis and Morel's disease in goats. *Veterinarski Arhiv 85*(2): 163-173.

Harwood, D., & Mueller, K. (2018). Goat medicine and surgery. EUA: CRC Press.

Heggelund, L., Gaustad, P., Håvelsrud, O. E., Blom, J., Borgen, L., Sundset, A., Sørum, H., Frøland, S. S. (2015). *Corynebacterium pseudotuberculosis* Pneumonia in a Veterinary Student Infected During Laboratory Work. *Open forum infectious diseases 2*(2): ofv053. doi:10.1093/ofid/ofv053.

Hernandez, L.F., Montes de Oca, J.R., Varela, G.J.A., Fernández, R.P., Salazar, G.F., & Monroy, S.H.G. (2019). Análisis filogenético en aislados de *Corynebacterium pseudotuberculosis* de casos clínicos de Linfadenitis caseosa en ovinos y caprinos. *Revista Acadêmica Ciência Animal 17*(1): 396-398.

Izgür, M., Akan, M., Ilhan, Z., & Yazicioglu, N. (2010). Studies on vaccine development for ovine caseous lymphadenitis*****. *Üniversitesi Veteriner Fakültesi* 57: 161-165. doi:10.1501/Vetfak_0000002371

Jeber, Z.K.H., MohdJin, Z., Jesse, F.F., Saharee, A.A., Sabri, J., Yusoff, R., & Wahid, H. (2016). Influence of *Corynebacterium pseudotuberculosis* infection on level of acute phase proteins in goats. *BMC Veterinary Research 12*(48): 1-5. doi:10.1186/s12917-016-0675-y

Lefevre, P.C., Blancou, J., Chermette, R., & Uilenberg, G. (2010). Caseous lymphadenitis in sheep and goats: Infectious and Parasitic Diseases of Livestock. Francia: Tec & Doc.

Marques da Silva, W., Seyffert, N., Silva, A., & Azevedo, V. (2021). A journey through the *Corynebacterium pseudotuberculosis* proteome promotes insights into its functional genome. *PeerJ* 9, e12456. doi:10.7717/peerj.12456

Matthews, J. (2016). Diseases of the Goat. Reino Unido: John Wiley & Sons, Ltd.

Meng, W., Chen, S., Huang, L., Yang, J., Zhang, W., Zhong, Z., Zhou, Z., Liu, H., Fu, H., He, T., & Peng, G. (2023). Isolation, characterization, and pathogenicity assessment of *Corynebacterium pseudotuberculosis* biovar equi strains from alpacas (*Vicugna pacos*) in China. *Frontiers in microbiology* 14, 1206187. doi:10.3389/fmicb.2023.1206187

Nabih, A.M., Hussein, H.A., El-Wakeel, S.A., Abd El-Razik, K.A., & Gomaa, A.M. (2018). *Corynebacterium pseudotuberculosis* mastitis in Egyptian dairy goats. *Veterinary World. 11*(11): 1574-1580. doi:10.14202/vetworld.2018.1574-1580

Nicoleti, J. L., Façanha, D. A., Kalil, M. A., Fonseca, E. P., Barral, T. D., Sampaio, J. R., Meyer, R., & Portela, R. W. (2022). Hematological and clinical biochemistry profiles in Canindé goats infected by *Corynebacterium pseudotuberculosis* and bred in a tropical semi-arid region. *Tropical animal health and production 55*(1): 11. doi:10.1007/s11250-022-03431-0

Oreiby, A.F. (2014). Diagnosis of caseous lymphadenitis in sheep and goat. *Small Ruminant Research 123*(1): 160–166. doi:10.1016/j.smallrumres.2014.11.013

Oreiby, F.A., Osman, A.S., Hegazy, M., Ghanem, A.Y., & Al-Gaabary, H.M. (2013). Caseous Lymphadenitis in small ruminants: Descriptive, epidemiological and clinical studies. *Kafrelsheikh Veterinary Medical Journal* (11)1: 41-61. doi:10.21608/KVMJ.2013.110162

Parise, D., Parise, M. T. D., Viana, M. V. C., Muñoz-Bucio, A. V., Cortés-Pérez, Y. A., Arellano-Reynoso, B., Díaz-Aparicio, E., Dorella, F. A., Pereira, F. L., Carvalho, A. F., Figueiredo, H. C. P., Ghosh, P., Barh, D., Gomide, A. C. P., & Azevedo, V. A. C. (2018). First genome sequencing and comparative analyses of *Corynebacterium pseudotuberculosis* strains from Mexico. *Standards in genomic sciences, 13*(21). doi:10.1186/s40793-018-0325-z

Parise, D., Teixeira Dornelles Parise, M., Pinto Gomide, A.C., Figueira Aburjaile, F., Bentes Kato, R., Salgado-Albarrán, M., Tauch, A., Ariston de Carvalho Azevedo, V., & Baumbach, J. (2021). The Transcriptional Regulatory Network of *Corynebacterium pseudotuberculosis*. *Microorganisms 9*(2), 415. doi: 10.3390/microorganisms9020415.

Park, S., Shin, H., Kim, S., Lee, T., Lee, H., Nam, K., Yoon, W., Kim, H., Seo, Y., Won, Y., & Kwon, H. (2022). Distribution of *Corynebacterium* Species and Comparative Results of Diagnostic Methods for Identifying *Corynebacterium* in Experimental Mice in Korea. *Veterinary sciences, 9*(7), 328. doi: 10.3390/vetsci9070328.

Quiroga, V.D.B., Gutiérrez, H,J.L., Palomares, R.E.G., Herrera, L.E., Díaz, A.E. (2019). Evaluación de tres protocolos de extracción de ADN para el diagnóstico de linfadenitis caseosa mediante una técnica de reacción en cadena de la polimerasa múltiple (PCRm) en pequeños rumiantes. *Revista Acadêmica Ciência Animal 17*(1): 451-454.

Rebouças, M.F., Loureiro, D., Barral, T.D., Seyffert, N., Raynal, J.T., Sousa, T,J., Figueiredo, H.C.P., Azevedo, V., Meyer, R., & Portela, R.W. (2020). Cell wall glycolipids from *Corynebacterium pseudotuberculosis* strains with different virulences differ in terms of composition and immune recognition. *Brazilian journal of microbiology 51*(4): 2101-2110. doi: 10.1007/s42770-020-00343-9

Rezende, A.F.S., Brum, A.A., Reis, C.G., Angelo, H.R., Leal, K.S., Silva, M.T.O., Simionatto, S., Azevedo, V., Santos, A., Portela, R.W., Dellagostin, O., & Borsuk, S. (2016). In silico identification of *Corynebacterium pseudotuberculosis* antigenic targets and application in immunodiagnosis. *Journal of medical microbiology 65*(6): 521-529. doi: 10.1099/jmm.0.000263

Sá, A.M.C., Rocha, F,J.T., Sales, R.D., de Sá, O.S.A., Pereira, F.D., Alcantara, M.E., da Costa, M.M., & Meyer, R. (2018). Linfadenite caseosa em caprinos e ovinos: Revisão. *PUBVET 12*(11): 1-13. https://doi.org/10.31533/pubvet.v12n11a202.1-13

Schlicher, J., Schmitt, S., Stevens, M.J.A., Stephan, R., & Ghielmetti, G. (2021). Molecular Characterization of *Corynebacterium pseudotuberculosis* Isolated over a 15-Year Period in Switzerland. *Veterinary Science* 8: 1-14. doi: 10.3390/vetsci8080151

Selim, A. M., Atwa, S. M., El Gedawy, A. A., Hegazy, Y. M., Rizk, M. A., & Younis, E. E. (2021). Risk factors associated with the seroprevalence of caseous lymphadenitis in sheep. *Comparative Clinical Pathology 30*(2): 285-291. doi: 10.1007/s00580-021-03198-0

Seyffert, N., Guimarães, A. S., Pacheco, L. G., Portela, R. W., Bastos, B. L., Dorella, F. A., Heinemann, M. B., Lage, A. P., Gouveia, A. M., Meyer, R., Miyoshi, A., & Azevedo, V. (2010). High seroprevalence of caseous lymphadenitis in Brazilian goat herds revealed by *Corynebacterium pseudotuberculosis* secreted proteins-based ELISA. *Research in veterinary science 88*(1): 50-55.

Shi, J., Wang, Z., Wu, B., Li, X., Li, X., Tian, S., Wu, J., & Zhou, Z. (2019). Cofilin-1, peroxiredoxin-1, and galectin-3: Major proteins released by macrophages infected with *Corynebacterium pseudotuberculosis*. *Veterinary Microbiology 239*(2019). doi: 10.1016/j.vetmic.2019.108461

Silva, M.T.O., Bezerra, F.S.B., de Pinho, R.B., de Santana Ferreira, C., Vivas, W.L., Portela, R.W.D., Azevedo, V.A.C., & Borsuk, S. (2019). The combination of *Corynebacterium pseudotuberculosis* recombinant proteins rPLD, rCP01850 and rCP09720 for improved detection of caseous lymphadenitis in sheep by ELISA. *Journal of Medical Microbiology* 68: 1759-1765. doi: 10.1099/jmm.0.001096

Singh, D., Tanwar, M., Kachwaha, K., Gharu, S., Dager, K.C., & Bamaniya, M.K. (2016). Clinical diagnosis and surgical management of caseous lymphadenitis in goats (*Capra hircus*). *Veterinary Practitioner 17*(1): 103-104.

Sobrinho, E.M., Almeida, A.C., Santos, H.O., Cangussu, A.S.R., Almeida, D.A., & Costa, K.S. (2018). Leader gene of *Corynebacterium pseudotuberculosis* may be useful in vaccines against caseous lymphadenitis of goats: a bioinformatics approach. *Journal of Veterinary Medical Science* 80: 1317-1324. doi:10.1292/jvms.16-0581

Szwako, A., Ortíz, N., & López, D. (2014). Prevalencia de *Linfadenistis caseosa* (*Corynebacterium pseudotuberculosis*) en caprinos de establecimientos lecheros del departamento central - Paraguay, año 2012. *Compendio de Ciencias Veterinarias 4*(1): 24-29.

Tan, J., Yi, W., Wang, Z., Ye, C., Tian, S., Li, X., Zou, A., Zhao, X., Yuan, Y., Wang, X., Hu, S., & Zhou, Z. (2021). TRIM21 negatively regulates *Corynebacterium pseudotuberculosis*-induced inflammation and is critical for the survival of *C. pseudotuberculosis* infected C57BL6 mice. *Veterinary Microbiology* 261: 1-9. doi: 10.1016/j.vetmic.2021.109209

Tizard, I. (2018). Veterinary Immunology. EUA: Elsevier.

Tuemmers, C., & Saldivia, A. (2015). Dermatopatías bacterianas de importancia en medicina equina. *Sustainability Agri Food and Environmental Research 3*(4): 30-53.

Umer, M., Jesse, F.F.A., Mohammed Saleh, W.M., Chung, E.L.T., Haron, A.W., Saharee, A.A., Mohd Lila, M.A., Ariff, A.B., Mohammad, K., & Sharif, A. (2020). Histopathological changes of reproductive organs of goats immunized with *Corynebacterium pseudotuberculosis* killed vaccine. *Microbial Pathogenesis* 149: 1-12. doi: 10.1016/j.micpath.2020.104539

Valdivia, J.D.Z. (2015). Vida intracelular de *Corynebacterium pseudotuberculosis* [Tesis de doctorado]. España: Universidad de las Palmas de la Gran Canaria.

Viana, M.V.C., Figueiredo, H., Ramos, R., Guimarães, L.C., Pereira, F.L., Dorella, F.A., Karim, S.A., Salaheldean, M., Silva, A., Wattam, A., & Azevedo, V. (2017). Comparative genomic analysis between *Corynebacterium pseudotuberculosis* strains isolated from buffalo. *PLoS One* 12: 1-24. doi:10.1371/journal.pone.0176347

Washburn, K.E., Bissett, W.T., Waldron, D.F., & Fajt, V.R. (2013). Serologic and bacteriologic culture prevalence of *Corynebacterium pseudotuberculosis* infection in goats and sheep and use of Bayesian analysis to determine value of assay results for prediction of future infection. *Journal of the American Veterinary Medical Association 242*(7): 997-1002. doi: 10.2460/javma.242.7.997

Zamprogna, T. O., Ribeiro, D., Azevedo, V. A., Lara, G. H., Motta, R. G., da Silva, R. C., Siqueira, A. K., de Nardi Júnior, G., Listoni, F. J., de Souza Araújo Martins, L., da Silva, A. V., Portilho, F. V. R., da Rocha Mota, A., Rodrigues, C. A., de Almeida, B. O., & Ribeiro, M. G. (2021). Bacteriological, cytological, and molecular investigation of *Corynebacterium pseudotuberculosis*, mycobacteria, and other bacteria in caseous lymphadenitis and healthy lymph nodes of slaughtered sheep. *Brazilian journal of microbiology 52*(1): 431-438. doi:10.1007/s42770-020-00403-0

Zeru, F., & Kahsay, A.G. (2014). Caseous lymphadenitis in goats from Borena Range Land South Ethiopia slaughtered at Luna Export Abattoir. *Journal of Veterinary Medicine and Animal Health 6*(6): 168-173. doi: 10.5897/JVMAH2013.0251

Zhou, Z., Li, H., Tian, S., Yi, W., Zhou, Y., Yang, H., Li, X., Wu, B., Li, X., Wu, J., Wang, Z., Hu, S., & Fang, R. (2019). Critical roles of NLRP3 inflammasome in IL-1β secretion induced by *Corynebacterium pseudotuberculosis in vitro*. *Molecular Immunology* 116: 11-17. doi: 10.1016/j.molimm.2019.09.016