Received: 10 January 2022, Accepted: 11 March 2022

Review Article

Journal of Advanced Veterinary Research
(2022) Volume 12, Issue 2, 177-186

A Current Review on Mycolic Acid Immunogen of *Corynebacterium pseudotuberculosis*

Mohammed Naji Odhah[1,2,3], Faez Firdaus Abdullah Jesse[1,4*], Bura Thlama Paul[1,5], Eric Lim Teik Chung[6], Mohamad Nor Nur Faeza[7], Mohd Jefri Norsidin[1], Bashiru Garba[8], Mohd Azmi Mohd Lila[7]

[1]Department of Veterinary Clinical Studies, Faculty of Veterinary Medicine, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia.
[2]Department of Veterinary Clinical Studies, Faculty of Veterinary Medicine, Universiti Malaysia Kelantan (UMK), Pengakalan Chepa 16100, Kota Bharu, Kelantan, Malaysia.
[3]Department of Public Health, Faculty of Veterinary Medicine, Thamar University, 87246, Dhamar, Yemen.
[4]Institute of Tropical Agriculture and Food Security, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia.
[5]Veterinary Teaching Hospital, University of Maiduguri, 600230 Maiduguri, Borno State, Nigeria.
[6]Department of Animal Science, Faculty of Agriculture, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia.
[7]Department of Veterinary Pathology and Microbiology, Faculty of Veterinary Medicine, Universiti Putra Malaysia, Serdang, Selangor, Malaysia.
[8]Department of Veterinary Public Health and Preventive Medicine, Faculty of Veterinary Medicine, Usmanu Danfodiyo University, Sokoto, Nigeria.

***Correspondence**

Faez Firdaus Abdullah Jesse, Department of Veterinary Clinical Studies, Faculty of Veterinary Medicine, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia.
E-mail: jesse@upm.edu.my

Abstract

Caseous lymphadenitis (CLA) is a disease of sheep and goats caused by *Corynebacterium pseudotuberculosis*. Members of *Corynebacterium, Mycobacterium, Nocardia* and *Rhodococcus* are the CMNR group of bacteria, which are so-called because they possess an outer cell membrane containing mycolic acids (MAs). This outer membrane presumably acts as a permeability barrier that imparts high drug resistance levels to some members of this group. The distinguishing feature of *C. pseudotuberculosis* is that MAs and phospholipase D (PLD) encoded by a β-corynephage in its genome are putative carriers of the toxins. Almost all members of the CMNR group possess a mycolic acid layer or mycomembrane around the cell wall, which is the main virulence determinant and plays a vital role in bacterial survival. Both PLD and MAss are virulence factors that play crucial roles in the pathogenesis of *C. pseudotuberculosis*. Phospholipases are glycophospholipid-hydrolyzing enzymes that facilitate bacterial dissemination in the host and assist the bacteria to evade phagocytosis by depletion of complement and impaired chemotaxis of neutrophils. MAs are waxy coat that protects the bacterium from hydrolytic enzymes within lysosomes and enables bacteria to skip phagocytosis and survive within the host cell. This review presents current research information on the mycolic acids of *C. pseudotuberculosis* and their role in the pathogenesis of the disease which includes host cell responses of acute-phase proteins, pro-inflammatory cytokines, and reproductive hormones changes and cellular tissue changes.

KEYWORDS
Corynebacterium pseudotuberculosis, immunogen Mycolic acid, host cell, responses, acute phase proteins, pro-inflammatory cytokines, reproductive hormones and cellular changes.

BACKGROUND

Corynebacterium pseudotuberculosis is a small, non-spore-forming, curved, gram-positive, intracellular anaerobic rod-shaped bacterium that causes caseous lymphadenitis (CLA) among small ruminants (Collins *et al*., 1982; Dorella *et al*., 2009; Jesse *et al*., 2011; Odhah *et al*., 2017). The transmission of *Corynebacterium pseudotuberculosis* occurs through direct exposure to the bacterium via physical contact with the infected animal or indirectly through fomites contaminated with organisms released from rupture of abscesses (Stoops, and Thilsted, 1984; Collet *et al*., 1994; Jesse *et al*., 2008; Saad *et al*., 2013).

Corynebacterium diphtheria and *Corynebacterium pseudotuberculosis* belong to the suborder Corynebacterinae, which are pathogenic bacteria species enveloped in a waxy substance known as mycolic acids (MAs) (Daffé and Draper, 1997). The MAs are built in an intricate structural design that renders the bacteria cell membrane impermeable to external assaults (Damien *et al*.,

ISSN: 2090-6277/2090-6269/

2004; Jesse *et al*., 2013a). Mycolic acids are extracted using organic solvents such as glycerol or by esterification of the terminal Penta-arabinofuranosyl units of arabinogalactan (McNeil *et al*., 1991; Marrakchi *et al*., 2014; Faeza *et al*., 2019b). Mutant strains of *Corynebacterium* lack MAs (Portevin *et al*., 2004; Portevin *et al*., 2005; Zuber *et al*., 2008).

The chemical structure of MAs was first elucidated in 1950 (Asselineau and Lederer, 1950). Mycolic acids consist of 3-hydroxyl molecules, a feature that confers its property of being cleaved at extreme temperature, by a reaction similar to a reverse Claisen-type condensation, into a "mero" aldehyde main chain, also called a "meromycolic chain," and a "fatty acid" (Asselineau *et al*., 1970). Recently, structures of MAs of genera other than that of Mycobacteria were showed to be relatively simple in terms of chemical functions, composing only of a homologous series with various numbers of double bonds, with up to 6 for Tsukamurella species (Tomiasu and Yano, 1984; Butler and Guthertz, 2001). In contrast, MAs of Mycobacteria have chains that define MAs' different classes, leading to intricate TLC patterns (Minnikin *et al*., 1983; Barry *et al*., 1998; Burkovski, 2013;). Non-polar MAs referred to as α-MAs, contains about 74-80 carbon atoms and two double bonds. A fraction of α-MAs may contain unsaturation, as observed in some strains of the *M. tuberculosis* complex (Watanabe *et al*., 2001). Polyunsaturated α-MAs represents a significant portion of the MAs in *Mycobacterium fallax* and MAs with 60-62 carbon atoms, known as α MAs, contain one cis double bond. *Segniliparus* was recently shown to have an array of MAs with chain lengths like those of Mycobacteria (Butler *et al*., 2005; Hong *et al*., 2012; Laneelle *et al*., 2013).

Mycolic acids from most mycobacteria possess supplementary oxygen functions located in the distal part of the meromycolic chain, signifying the methoxy and keto MAs wax ester-, epoxy-, and hydroxy-types of MAs (Daffe *et al*., 1983). The oxygen functions occurring in mycobacterial MAs are typified by the occurrence of an adjacent methyl branch. It is worthy of mentioning that in *M. tuberculosis*, the oxygenated MAs, i.e., hydroxyl MAs and keto, methoxy, contain (84-88) carbon atoms, and are thus four to six carbons longer than the α-MAs from the same strains (Laval *et al*., 2001; Faeza *et al*., 2019a). However, there is still a lack of information on the mechanism of action and host cell responses towards Mycolic acid (Carne, 1939; Onon, 1979).

The exotoxin of the bacteria which act as the virulence factor contributes to the penetrability factor for the establishment of the infection in the infected host. In addition to that, mycolic acid and phospholipase D causes necrosis of endothelial cell which contributes to the movement of *C. pseudotuberculosis* through the skin reaching other minute blood vessels supplying the lymph vessels (Egen *et al*., 1989; Songer, 1997; Komala *et al*., 2008; Odhah *et al*., 2017). Furthermore, phospholipase D exerts cytotoxic effects on leukocytes and enhances the lysis of macrophages experimentally challenged goats (Mahmood *et al*., 2015b). The previous study done using specific anti phospholipase D antibodies showed that exotoxin was essential for the occurrence development of CLA in the host. Vaccination of goats and sheep with inactivated exotoxins prevented the infiltration of bacteria experimentally (Brown *et al*., 1986). Phospholipase D and MAs serves as determinants of virulence of *C. pseudotuberculosis* because the progeny of PLD-knocked bacteria were unable to produce typical CLA lesion but instead an immunologic reaction (Fontaine and Baird, 2008; Faeza *et al*., 2019b). These findings suggested that the mutant bacteria may be utilized as a live vaccine specimen for CLA (Hodgson *et al*., 1992). On the other hand, the virulence status of PLD activity can be demonstrated by the induction of skin necrosis, and direct damage to the "endothelial" cells. Phospholipase D works "synergistically" with cholesterol oxidase through hydrolysis, and this combined role results in β-hemolysis of small ruminant red blood cells by *Rhodococcus equi* (Bastos *et al*., 2012). The phosphate ceramide produced during transition is hydrolyzed by phospholipase C of *Rhodococcus equi* (Brown *et al*., 1987; Pawełczyk and Kremer, 2014). *Corynebacterium pseudotuberculosis* is an intracellular bacterium that multiplies in macrophages and survives by resisting the activities of phagolysosomes due to the cell walls which consist of an external lipid layer. As a result, this facilitates the spread of bacteria into the lymphatic system and the regional lymph nodes (Dorella *et al*., 2006a; Baird and Fontaine, 2007). After penetration of the causative organism into the host through the nasal cavity, mouth, and ocular mucosa or through the skin, the organism spreads freely or within the macrophages to invade the lymph and reach the internal organs and local lymph nodes (Faeza *et al*., 2019a; Jesse *et al*., 2020). The pathogenicity of *C. pseudotuberculosis* depends on its efficiency to affect macrophages, halt phagolysosome activity, and cause tissue necrosis (Batey, 1986a; Jesse *et al*., 2013b). On the other hand, further spread of the organism from the primary site of entry to the location of CLA lesion depends upon its survival and recurrence within the macrophages facilitated by mycolic acid (Baird and Fontaine, 2007; Jesse *et al*., 2011). The pyogenic lipid cell layer of the organism is immunogenic and inhibits phagocytosis by elevating its cytotoxicity and destruction of macrophages in abscesses by the release of lysosomal enzymes. It has also been reported that the participating mycolic acid in pathogenicity proves relevant for bacterial survival (Fontaine and Baird, 2008; Stefánska *et al*., 2010). Due to the paucity of knowledge and the gap of CLA, this review focused on the current findings on mycolic acid from *C. pseudotuberculosis* towards host cell responses such as reproductive hormones, pro-inflammatory cytokines, acute-phase protein and cellular changes.

Corynebacterium pseudotuberculosis

General Characteristics of C. pseudotuberculosis

Corynebacterium pseudotuberculosis has been studied for generations dating back to 1888 when it was first discovered by a French bacteriologist named Edward Nocard who identified it as a peculiar organism isolated from an incidence of lymphatic vessels in a cow. Three years later, Hugo V. P., a bacteriologist from Bulgaria isolated a similar organism from a case of kidney abscess in a ewe and the bacterium was named "Preisz-Nocard" bacillus (Baird and Fontaine, 2007; Papaioannou *et al*., 2010). In 1948, the bacterium was renamed *C. pseudotuberculosis* which has remained its official designation even though some works of literature still refer to it as *Corynebacterium ovis* (Euzéby, 2003; Euzéby *et al*., 2004).

C. pseudotuberculosis is a pathogen of socio-economic importance responsible for caseous lymphadenitis (Jesse *et al*., 2008) with a significant economic loss towards the farmer. Globally, this disease is of serious importance as it is found threatening the production of sheep and goats (Baird and Fontaine, 2003; Latif *et al*., 2015) with high morbidity resulting in wool loses, milk and meat devaluation hence economic downturn for the farmers (Paton *et al*., 2003; Paton 2010). In many countries, this disease is still an important problem that is affecting the small ruminant and mutton industry (Ribeiro *et al*., 2013).

The organism has been isolated from sheep and goats had been done (biovar ovis) and some reports indicate that it can also be isolated from horses and cattle (biovar equi) (Dorella *et*

al., 2006b; Latif *et al*., 2015). Many researchers have defined related bacteria from bovine lymphangitis (Yeruham *et al*., 1996) and ovine renal abscesses (Baird and Fontaine, 2007). So far, the bacterium has been isolated from ulcerative lymphangitis and purulent infections in man and some mammalian species such as goats, horses, and cattle (Corbeil, 2016).

The phylogenic classification of C. pseudotuberculosis

Corynebacterium pseudotuberculosis is a member of the genus *Corynebacterium*, which belongs to the family *Corynebacteriaceae*, sub-order *Corynebacterinae* in the order *Actinomycetales*, sub-class *Actinobacteridae* and class *Actinobacteria* (Stackebrandt *et al*., 1997). This and other genera like the *Mycobacterium, Nocardia* and *Rhodococcus* are the entire *Actinomycetes* group (Dorella *et al*., 2006a; Jesse *et al*., 2008). The *Corynebacterinae* of the genera dominates the group of CMNR, which share several common features such as cellular organization, consisting of majorly the mycolic acids, peptidoglycans with a reasonable amount of guanine and cytosine genomically. The CMNR group encompasses other species of importance to both the Veterinary and Medical world, which include *M. tuberculosis*, M. leprae and M. bovis. *Corynebacterium pseudotuberculosis* is further sub-classified into two: the biovar ovis, which is generally incriminated in the sheep and goats resulting in an abscess in the viscera and superficial tissues (Biberstein *et al*., 1971). The second is the biovar equi affects equine species and is characterized by ulcerating lymphangitis around the distal extremities, abdominal and thoracic abscesses. The biomolecular technique was used to establish these two biovars (Sutherland *et al*., 1996; Costa *et al*., 1998; Connor *et al*., 2000; Connor *et al*., 2007).

Biochemical characteristic and virulence factors of C. pseudotuberculosis

C. pseudotuberculosis can ferment a variety of oligosaccharides such as galactose, mannose, glucose, and maltose (Henderson, 1979; Jesse *et al*., 2013a). It also produces and releases different enzymes (Pazatsen *et al*., 2012). Remarkably, these biochemical properties are indistinguishable among all *C. pseudotuberculosis* strains isolated from many animal species (Sutherland *et al*., 1996; Abdullah *et al*., 2013). The oxidation of nitrate to nitrite is a unique biochemical character (Foley *et al*., 2004). One of the major challenges for *C. pseudotuberculosis* is probably achieving the synthesis of this thick multilayer barrier (Burkovski, 2018). The *C. pseudotuberculosis* envelope is partly responsible for its innate resistance to antibiotics and plays a major role in both its virulence and persistence (Oliveira *et al*., 2017).

It has been described that *C. pseudotuberculosis* strains collected from some equine and bovines were consistently capable of reducing nitrate. On the other hand, the strains collected from ovine and caprine do not reduce nitrate (Latif *et al*., 2017). Thus, the nitrate-negative *C. pseudotuberculosis* strains, which are pathogenic in the goats and sheep, were apportioned to biotype I, while nitrate-positive strains, which infect horses and cattle, were apportioned to biotype II (Sutherland *et al*., 1996; Butler *et al*., 2005). Serotyping (Barak *et al*., 1992), molecular analysis (Muckle *et al*., 1992) and immunoblotting (Perkins *et al*., 2004) are useful methods to characterize strains of *C. pseudotuberculosis*. The molecular analyses are important in supporting the biochemical findings of two different biovars of *C. pseudotuberculosis* (Khuder *et al*., 2012).

Several studies on the virulence factors or determinants of most bacterial species had yielded a lot of information but there is a paucity of data on the virulence determinants of *C. pseudotuberculosis* (Jesse *et al*., 2020). In recent times, few molecular studies had tried to explain the genetics of *C. pseudotuberculosis* about the identification of two virulent factors including Mycolic acids (MAs) and Phospholipase D (PLD) (Baird and Fontaine, 2007; Mahmood *et al*., 2015b; Odhah *et al*., 2019).

Structure of Mycolic acids

Corynebacterium has a complex cell wall structure which is considered as the main virulence determinant (Butler *et al*., 1986; Collins *et al*., 1988). This complex cell wall structure is called the mycolic acid or corynomycolic acids (Minnikin *et al*., 1983). They are characterized by a 2-branched 3-hydroxy fatty acid long-chain and represented the shortest lipid in the group extending twenty and thirty-six carbon atoms in their lengths (Alshamaony *et al*., 1977; Goodfellow *et al*., 1982; González *et al*., 2011). In contrast, Mycobacterial corynomycolic acids extend between sixty and ninety carbon atoms in length (Ioneda and Silva, 1979; Ioneda, 1989). These lipid structures in *C. pseudotuberculosis* are the main virulence determinants and they play a vital role in bacterial survival (Bastos *et al*., 2012). The lipid nature of this mycolic acid is responsible for its cytotoxic effects (Hard, 1975). It had been indicated that the mycolic acid after purification and inoculation in mice models elevated the clinical signs and resulted in localized congestion, oedema, and hemorrhagic necrosis (Gotoh *et al*., 1991; Nieto *et al*., 2009).

In addition, mycolic acids exhibit inflammatory regulatory features, a distinct response that was tolerogenic had been reported in experimental asthmatic conditions, but the chemical constituent is heterogenic (Korf *et al*., 2006). In vitro studies have shown white blood cell (WBC) degeneration in phagocytosis of these bacteria (Peyron *et al*., 2008). *Corynebacterium pseudotuberculosis* has the cellular capacity to withstand phagocytic activities of antigen-presenting cells. In pathogenic bacteria, MAs have long been known to induce inflammatory responses and granuloma formations and functions as an adjuvant for T cell responses (Kim *et al*., 2014; Odhah *et al*., 2017). A lot of research showed that the virulence factor of *C. pseudotuberculosis* is related to its cell wall lipid contents (Muckle and Gyles, 1983). Based on their studies, the presence of mycolic acid in the cell wall of these bacteria enables it to exert its pathogenic effects and survive as an intracellular bacterium (Dubnau *et al*., 2000) despite the well-established fact that lysosomes have the lysing ability on any invading organism. However, *M. tuberculosis* survives within the agranulocytes when it is engulfed (Bhatt *et al*., 2007).

Mycolic acid in Corynebacterium pseudotuberculosis

The members of this heterogeneous group share certain characteristics, such as a specific cell wall organization and high guanine and cytosine content on the genome. The cell walls of these genera are composed of a huge polymer complex of peptidoglycan and arabinogalactan and are rich in complex lipid components. The best characterized of these lipids is a long-chain 2-branched 3-hydroxy fatty acid, commonly known as mycolic acid. The mycolic acids of the *Corynebacterium*, also known as corynomycolic acids, are the shortest of the group, being between 20 and 36 carbon atoms in length, whereas those of *Mycobacterium* ranges between 60-90 (Brown and Olander, 1987; Dorella *et al*., 2006a). The corynomycolic acid is an important virulence factor of *C. pseudotuberculosis* as they contribute to its high tenacity and its ability to persist as a facultative intracellular parasite (Baird, 2003). Two different biovars of *C. pseudotuberculosis* can be dis-

tinguished based on the different nitrate reduction abilities of the two biotypes. Strains isolated from small ruminants tend not to reduce nitrate to nitrite whereas isolates from horses and cattle almost invariably possess a nitrate-reductase and are, therefore, able to reduce nitrate. Thus, Biberstein (1971) suggested the separation into the two biovars *C. pseudotuberculosis* biovar *equi* and *C. pseudotuberculosis* biovar *ovis*. There is a paucity of information in previous literature related to the extracted MAs from *C. pseudotuberculosis* towards the host cell responses such as in clinical signs, haemogram analyses, acute phase proteins (SAA and Hp) responses, antibody (IgM and IgG) titers, reproductive hormones (E2 and P4) concentrations, histopathology cellular changes in vital organs, reproductive organs, bone marrow and its associated lymph nodes.

Structure of Phospholipase D (PLD)

Phospholipase D is an enzyme that belongs to a group of lipases, which can hydrolyze the ester bonds in glycerophospholipids. The letter D indicated the specific ester bond that is targeted or cleaved. In general, phospholipase as an enzyme plays a vital role in the maintenance of cell membrane and signal transduction in eukaryotes (Abra and Quinn, 1975; Abdullah *et al*., 2015). Barksdale *et al*. (1981) were the first to describe PLD from *C. pseudotuberculosis*. Later, it was found in almost all isolates of *C. pseudotuberculosis* including biotypes I and II from all species of mammals that were infected with *C. pseudotuberculosis* (Songer *et al*., 1988). The fact that PLD is a risk factor had been established with some isolates of *C. pseudotuberculosis* that had their PLD genes encoding PLD attenuated as they could not cause abscess formation in the lymph nodes of the infected sheep (McNamara *et al*., 1994; Latif *et al*., 2015). PLD hydrolyzes phosphatidylcholine and sphingomyelin found on the cell membranes of mammals, thereby forming choline and ceramide phosphate (Carne, 1939; Onon, 1979). The exotoxins of the bacteria functions as a permeability factor that promotes the systemic dissemination of the pathogen (Jesse *et al*., 2013a).

In addition, PLD results in the dermal necrosis of cells in the endothelial lining easing *C. pseudotuberculosis* passage into small blood vessels, thereby gaining entrance into the lymphatic vessels (Egen *et al*., 1989; Songer, 1997). PLD is regarded as a cytotoxic exotoxin for WBC because it destroys the goat macrophages during laboratory trial (Tashijian and Campbell, 1983; Mahmood *et al*., 2015a). Vaccination of goats with the toxin also prevented the spread of the bacteria after an experimental challenge (Brown *et al*., 1986; Jesse *et al*., 2020). PLD mutants are virulence factors of *C. pseudotuberculosis* as they did stimulate an immune response. The bacterial spread by PLD action is explained by dermal necrosis which damaged the endothelial cells. It had also been reported that PLD during hydrolysis works synergistically with an oxidase of cholesterol and the C phospholipase both of which a product of *Rhodococcus equi* to produce in sheep a WBC β-hemolysis. A product ceramide phosphate is produced which gets hydrolyzed by the C phospholipase of *R. equi*, producing ceramide (Jolly, 1965; Brown and Olander, 1987). Dissociation of sphingomyelin into phosphate and choline is done by a sphingomyelin-specific phospholipase (Pepin *et al*., 1994). It participates in dermal necrosis (Catherine, 1994), macrophage destruction and interferes with neutrophil in goats (Yozwiak and Songer, 1993), synergistic hemolytic action in the presence of *Rhodococcus equi* extracellular factor (Fraser, 1961), inhibits hemolytic action induced by β-lysin produced by Staphylococcus. The two latter activities of PLD have been used in laboratories to identify *C. pseudotuberculosis* and thus, diagnose CLA (Zaki, 1976; Jesse *et al*., 2016). Phospholipase D hydrolyses sphingomyelin in mammalian cell membranes increasing the vascular permeability especially the endothelial layer, leading to plasma proteins leakage from the blood into the surrounding tissue space and from there into the lymphatic system (Mahmood *et al*., 2015a). This contributes to the dissemination of *C. pseudotuberculosis* from the primary infection location to other parts of the animal's body (Guimarães *et al*., 2009; de Sá Guimarães *et al*., 2011).

Pathogenesis of C. pseudotuberculosis

The pathogenesis of CLA in sheep and goats is still poorly understood. To date most research conducted focused on two known virulence factors of *C. pseudotuberculosis*; the phospholipase D and the mycolic acids (Mahmood, *et al*., 2016; Jesse, *et al*., 2020). Phospholipases are glycophospholipid-hydrolyzing enzymes that play an important role in signal transduction and the inflammatory response in eukaryotic cells. Many bacterial pathogens such as *Clostridium perfringens* and *Listeria monocytogenes* produce phospholipases as a part of their invasive strategy (Songer, 1997). *Corynebacterium pseudotuberculosis* produces phospholipase D (PLD), a phosphatidylcholine phosphatidohydrolase that functions as a sphingomyelinase and catalyze the repulsion of sphingomyelin to choline and ceramide (Pepin *et al*., 1994).

PLD is a virulence factor since *C. pseudotuberculosis* isolates in which the PLD gene was deleted from the genome were incapable of progressing from the site of infection and could not produce the classic lymph node abscesses (Pepin *et al*., 1994; Jeber *et al*., 2016). Dermonecrosis, lethality and synergistic lysis of erythrocytes in the presence of *Rhodococcus equi* exotoxin have been reported due to PLD (Pepin *et al*., 1994; Baird and Fontaine, 2007). Jolly (1965) showed that PLD functions as a permeability factor that increases vascular permeability and causes the leakage of plasma from the vessels through hydrolysis of sphingomyelin in endothelial membranes. This effect may assist in pathogenesis by allowing the bacteria to disseminate from the site of infection to the local lymph nodes (Brown and Olander, 1987; Pepin *et al*., 1994). This hypothesis was supported by Zaki (1976), who showed that antibodies against the toxin prevented the dissemination of the bacterium from the portal of entry. He concluded that the exotoxin, while not involved in the formation of abscesses, was crucial for the spread of the organism.

Furthermore, PLD may assist *C. pseudotuberculosis* in avoiding phagocytosis early in infection as it was shown to activate complement, and thus deplete it from the surrounding area, as well as impair the chemotaxis of neutrophils (Pepin *et al*., 1994; Osman *et al*., 2012b). Since it can replicate within and escape from macrophages, many researchers have suggested that the PLD might also be of significance in the escape from the phagosome and macrophage death (Pepin *et al*., 1994; McKean *et al*., 2007; Adza-Rina *et al*., 2013). The coat of waxy mycolic acids on the cell surface of *C. pseudotuberculosis* plays a major role in pathogenesis where it provides succour to the organism mechanically and biochemically. It has therefore been stipulated that MAs coat also aid the bacterium to extended survival periods which is synonymous with *Actinomycetales* and particularly *Mycobacterium* (Baird and Fontaine, 2007). *Corynebacterium pseudotuberculosis* has environmental resistance and shows a high tenacity in organic material (Augustine and Renshaw, 1986).

However, the cell surface lipid also protects the bacterium from hydrolytic enzymes within lysosomes which enables it to skip phagocytosis and survive within the host cell (Hard, 1972; Brown and Olander, 1987; Williamson, 2001). Pazatsen *et al*. (2012) first labelled *C. pseudotuberculosis* as a facultative intra-

cellular parasite. He infected mouse macrophages intraperitoneally with *C. pseudotuberculosis* and examined the ultrastructural changes using electron microscopy and observed that five minutes after infection, the bacteria were already engulfed by the macrophages and could be found in large vacuoles surrounded by an electron-dense layer, which was identified as the cell surface lipid of *C. pseudotuberculosis*. Furthermore, the study showed that macrophages that had ingested bacteria underwent rapid degeneration and cell death, releasing bacteria into the extracellular space where the bacteria remained intact. This study concluded that *C. pseudotuberculosis* can survive within the phagolysosomes and causes the death of its host cells due to the toxic effect of its surface lipid (Hard, 1972; Hard, 1975). Tashijian and Campbell (1983) confirmed this hypothesis in an electron microscopy study using caprine mammary macrophages infected with *C. pseudotuberculosis*. They observed that, despite the fusion of macrophage lysosomes with phagosomes containing bacteria, the caprine macrophages underwent progressive degeneration while the bacteria survived (Baird and Fontaine, 2007). The capacity to survive and replicate within phagocytic cells is crucial for the pathogenesis of *C. pseudotuberculosis* and it is thought that the organism migrates within macrophages from the entrance to the site of lesion development (Odhah *et al*., 2017). There is a consensus amongst researchers that *C. pseudotuberculosis* does not establish a persistent infection at the site of entry but disseminates rapidly, both as free bacteria and within macrophages, to the local lymph nodes (Ayers, 1977; Batey, 1986b; Pepin *et al*., 1991b). Pepin *et al.* (1991b) showed that a significant number of neutrophils were first mobilized to the site of infection and began appearing shortly afterwards in the local lymphatic drainage while the number of macrophages in the lesions rose dramatically on the third day after infection. As *C. pseudotuberculosis* can survive phagocytosis, the phagocytic cells serve as vehicles for transporting the bacterium into the local lymph nodes.

Additionally, the PLD exotoxin enhances the transfer of the bacterium via the lymphatics by inducing an inflammatory response and increasing the vascular permeability and lymph flow (Batey, 1986b; Pepin *et al*., 1991a; Mahmood *et al*., 2015a). Upon dissemination of the bacterium, micro-abscesses forms in the local lymph node, where, after an initial phase of neutrophil dominance, macrophages infiltrate the lesions (Pepin *et al*., 1991b; Othman *et al*., 2014a). Even though the macrophages are the main effector cells fighting *C. pseudotuberculosis*, they are not able to eliminate the pathogen. A cycle of phagocytosis, intracellular multiplication and death of the host cells starts, leading to the transformation of the abscesses into epithelioid cell granulomas with a central area of necrosis surrounded by a rim of epithelioid cell and fibrous tissue (Abdullah *et al*., 2015; Latif *et al*., 2017). As seen in other intracellular pathogens, the formation of granulomas results in the encapsulation and entrapment of the lesions but also provides the basis for the chronic nature of the disease. Since the bacteria remain viable in the granulomas, the animals are not able to eliminate the infection and often remain life-long carriers. Occasionally, bacteria escape from the abscesses, possibly through emigration of infected phagocytic cells, and spread further through the blood or lymphatic system to other lymph nodes where they are retained in smaller blood vessels and cause the formation of new lesions (Batey, 1986a; Pepin *et al*., 1991b). Additionally, the cytotoxic properties of the surface lipid directly contribute to abscess formation. The subcutaneous injection of mycolic acids elicits an inflammatory response, resulting in localized swelling and central haemorrhagic necrosis, and induces sterile pyogenic lesions (Hard, 1975; Ayers, 1977; Baird and Fontaine, 2007; Mahmood *et al*., 2016). Catherine (1994) also demonstrated a straight relationship existing between cell surface lipid quality of *C. pseudotuberculosis* and its power to induce a chronic abscess formation.

The resistance of host cell to C. pseudotuberculosis

The resistance of host cell to *C. pseudotuberculosis* infection is a complex process that involves the innate and acquired immune response (Zaki, 1976; Batey, 1986a; El-Enbaawy *et al*., 2005; Moura-Costa *et al*., 2008; Jesse *et al*., 2020). The significance of humoral defence had been elucidated by assessing various commercial and experimental vaccine (Eggleton *et al*., 1991; Stanford *et al*., 1998; Pinho *et al*., 2009), bacterial cell-wall fractions (Braga *et al*., 2007; Brogden *et al*., 1984), attenuated and killed bacteria (Simmons *et al*., 1997; Cameron *et al*., 1998), exotoxins and their subunits (Tashijian and Campbell, 1983) or genetically modified pathogens (Chaplin *et al*., 1999; De Rose *et al*., 2002). Significant advances in the field of vaccine production were an effective reduction in the formation of granulomas in experimentally challenged animals during trials. However, for adequate control of infection, macrophagic activation must be improved. A study using mice as a model indicated the potency of levamisole to evoke immunity against *C. pseudotuberculosis*. This finding suggests that cell-mediated immunity might play a significant role in *C. pseudotuberculosis* (Irwin and Knight, 1975). The participation of the complement system in *C. pseudotuberculosis* was studied in experiments demonstrating that type 3 complement receptor (CR3) played a key role during the infection. The findings indicated that treatment of mice with an anti-CR3 mAb resulted in the bacterial proliferation in both liver and spleen with a quite dramatic rise in the amount of mortality recorded 3 days post-infection. Histological investigations revealed that no mononuclear phagocytes gathered at the sites of bacterial proliferation and this confirms the importance of CR3 in the resistance *C. pseudotuberculosis* infection in mice (Lan *et al*., 1999).

Host Cell Responses to C. pseudotuberculosis and MAs

Acute phase protein responses toward C. pseudotuberculosis and its MAs

Acute-phase proteins (APPs) are a specialized group of blood proteins that would change in concentration in animals when subjected to external or internal challenges such as infection, inflammation, surgical trauma, or stress (Abdullah *et al*., 2013). Therefore, quantification of their concentration can provide diagnostic and prognostic information as biomarkers. The APPs are a composite of negative and positive protein that shows a falling or rising concentration during the response to challenge, respectively. The negative APPs include albumin and transferrin while haptoglobin (Hp), C-reactive protein, serum amyloid A (SAA), fibrinogen and alpha-l-acid glycoprotein are positive APPs. Haptoglobin and SAA are the major APPs in ruminants which can increase over 100-fold on stimulation (Skinner, 1991; Tothova *et al*., 2014). The acute phase proteins are synthesized by the liver and released following stimulation by cytokines. In ruminants, Hp and SAA are the major APPs that can increase up to 1,000-fold upon stimulation. The acute phase proteins are important in quantifying pathogenesis level in experimental studies and field infection (Abdullah *et al*., 2013). Odhah *et al*. (2018) and Faeza *et al*. (2019a) stated that the acute phase proteins can be used as diagnosis and prog-

nosis markers for various inflammatory diseases, organ malfunction, and infectious diseases in ruminant livestock. Ewes infected with intrauterine bacterial postpartum contamination showed a significant increase in Hp, SAA and fibrinogen concentrations (Jesse *et al*., 2016; Faeza *et al*., 2019a). Mahmood *et al*. (2016) stated that Hp concentration was higher than SAA concentration in goats infected with *C. pseudotuberculosis* and challenged with its exotoxin PLD. In another study, Odhah *et al*. (2018) showed that a significant increase of Hp concentrations was observed in does challenge with *C. pseudotuberculosis* and its mycolic acid .

Pro-inflammatory cytokine responses toward C. pseudotuberculosis and its MAs

Pro-Inflammatory cytokines are produced by activated macrophages as a proprotein, which is proteolytically processed to its active form by caspase 1. This cytokine is an important mediator of the inflammatory response and is involved in a variety of cellular activities, including cell proliferation, differentiation, and apoptosis (Ingman and Jones, 2008; Jesse *et al*., 2016). Pro-inflammatory interleukins are polypeptides produced mainly by the WBC, which regulate immunity and inflammatory conditions. They stimulate pathological and physiological function containing non-specific immunity and specific immunity with an overabundance of inflammatory responses (Sirotkin, 2011; Jesse *et al*., 2017a). Interleukin-1β, interleukin-6, and tumour necrosis factor-α (TNF-α) are the pro-inflammatory cytokines that showed a significant increase of concentration in goats challenged with *C. pseudotuberculosis* and its MAs (Jesse *et al*. 2017b; Odhah *et al*., 2019). Concentrations of IL-1β and IL- 6 increased significantly in non-pregnant female goats challenged with *C. pseudotuberculosis* and MAs via the intradermal route (Jesse *et al*., 2017a). Another study by Faeza *et al*. (2019a) stated that bucks challenged with *C. pseudotuberculosis* and its MAs were able to stimulate the responses of IL-1β and IL-6.

Cellular responses towards C. pseudotuberculosis and its MAs

Lymph node enlargement is the main indicator of intracellular infectious diseases (Jesse *et al*., 2020) which can be seen in *C. pseudotuberculosis* as it causes pain (Latif *et al*., 2017). James and Zumla (1999) postulated that granulomas do not define the disease condition but tend to give an idea of the disease because of the characteristics of the pathogenic species. The infections by *C. pseudotuberculosis* cause inflammation of superficial lymph nodes because of systemic infection (Pepin *et al*., 1991a; Timoney *et al*., 1988). The common primarily infected superficial lymph nodes in CLA are the retropharyngeal, mandibular, parotid, prescapular, popliteal, mammary, and inguinal lymph nodes (Baird, 2003; Batey *et al*., 1986b; Roberson *et al*., 2012). The morphological changes commonly observed are granuloma containing bunches of histocytes with eosinophilic cytoplasm (Carrington *et al*., 1969; Dorella *et al*., 2006b; Khuder *et al*., 2012). Adza Rina *et al*. (2013) stated that goats challenged with live *C. pseudotuberculosis* through the intranasal route developed abscesses in the mesenteric and supra-mammary lymph nodes compared to oral and intradermal routes.

Kim *et al*. (2014) reported that treatment with mycolic acid immunogen depleted the T cells in the spleen and suppressed broncho alveolar inflammations, pulmonary inflammations, and asthmatic responses. Khuder *et al*. (2012) reported histopathological changes such as degeneration, congestion, necrosis, infiltration of polymorphonuclear leukocytes, haemorrhage, oedema and thrombus in the ovaries, uterus, testes, and epididymis in goats challenged with *C. pseudotuberculosis* and its exotoxin PLD. According to Al-Gaabary *et al*. (2010), the affected lymph nodes showed lesions of abscessation with a central zone of caseous necrosis surrounded by inflammatory cells consisting of a mixture of neutrophils and macrophages encapsulated by thick fibrous tissues and the liver section showed distorted necrosis in CLA infected sheep. Ibtisam (2008) explained that sheep infected naturally with *Corynebacterium pseudotuberculosis* exhibited abscess and pleural thickening with caseous material at the middle encapsulated by a zone of living and dead neutrophils in the lung whereas in the liver had evidence of congestion with a vacuolar degenerative change of hepatocytes. The heart showed congestion of blood vessels and haemorrhage with severe necrosis of myocardial fibres. The kidneys showed haemorrhage and degeneration of the cells lining the renal tubules. Mice challenged with *C. pseudotuberculosis* infection showed cellular changes in the ovary and uterus such as oedema, congestion, infiltration of neutrophil, macrophages, degeneration, and necrosis. The testis and epididymis exhibited cellular lesions such as oedema, congestion, degeneration, necrosis, and infiltration of polymorphonuclear leukocytes (Jesse *et al*., 2020). Latif *et al*. (2017) and Othman *et al*. (2014b) reported that does challenge with *C. pseudotuberculosis* showed cellular changes such as thrombus formation and necrosis in ovaries, vagina, uterus, and uterine horns. Faeza *et al*. (2019b) stated that bucks challenged with *C. pseudotuberculosis* and its MAs revealed significant and relatively new findings of cellular changes in testes and epididymis of both challenged groups.

Reproductive hormone responses towards C. pseudotuberculosis and its MAs.

Sex hormones play a vital role in male and female reproductive physiology by coordinating cell differentiation, proliferation, inflammation, apoptosis, homeostasis, and brain functioning (Edwards, 2005; Abdullah *et al*., 2015; Jesse *et al*., 2020). Sex hormones are produced by the gonads (testes and ovaries) and transported via the blood pool to act on the peripheral target tissue and the central nervous system (Wilson *et al*., 1998; Othman *et al*., 2014c). *Corynebacterium pseudotuberculosis* infection may cause inflammation and lead to the disruption of the hypophyseal-pituitary-gonadal axis (Jesse *et al*., 2017b). Several studies reported significant histopathological changes from mild to moderate severity in the pituitary gland, ovarian, cervix, uterus, fallopian tube, testes, spermatic and epididymis tissues in goats challenged with wild *C. pseudotuberculosis* and MAs (Khuder *et al*., 2012; Odhah *et al*., 2019; Faeza *et al*., 2019b). A recently published study by Jesse *et al*. (2020) reported significant cellular changes in the reproductive organs and their associated lymph nodes and changes in the reproductive hormones (estrogen and progesterone) in nonpregnant does experimentally infected with *C. pseudotuberculosis* and its MAs via intradermal routes. Khuder *et al*. (2012) described a significant decrease in plasma testosterone concentration in mice challenged with *C. pseudotuberculosis* and its exotoxin PLD. Faeza *et al*. (2019a) reported that male goats challenged with *C. pseudotuberculosis* showed lesions of the irregular shape of testes and shrinkage of seminiferous tubules with interstitial oedema and a significant decrease of testosterone hormone concentration were observed. In another study by Khuder *et al*. (2012) where male goats challenged with *C. pseudotuberculosis* and its exotoxin PLD showed a significant decrease in scrotal circumference, plasma testosterone concentration and semen quality parameters. A study by Umer *et al*. (2020) stated that male and female goats challenged with *C.*

pseudotuberculosis showed significant reproductive tissue damages in testes, epididymis, spermatic cord, penis, vulva, vagina, cervix, uterus, fallopian tubes, and ovaries. Abdullah *et al*. (2015), Khuder *et al*. (2012) and Jesse *et al*. (2020) described significant changes in reproductive hormones such as luteinizing hormone (LH), follicle-stimulating hormone (FSH), progesterone, estrogen and testosterone in animals infected with *C. pseudotuberculosis* and its immunogens exotoxin PLD and MAs.

CONCLUSION

In conclusion, this review has summarized the current information and research on mycolic acid from *C. pseudotuberculosis* and its interaction and responses of the host cell in terms of haematology, reproductive hormones, the acute-phase proteins, pro-inflammatory cytokines responses and cellular changes. *C. pseudotuberculosis* can colonise the reproductive tract in males and females and penetrate the physical barrier of the genital tract and cause severe tissue lesions in the vagina and iliac lymph node. Though there remains a dearth of information on the reproductive hormonal influence in female goats. Moreover, the causative agent of CLA reaches an effect on APP, and cytokines through lymphatic ways in infected goats. The review demonstrated that both microbiological and molecular techniques are useful tools in CLA and MAs. Therefore, future studies must be conducted on the *C. pseudotuberculosis* and its immunogens MAs effect on the various parts of the organs system and its physiological changes.

ACKNOWLEDGMENTS

The authors are grateful to officers of UPM Veterinary Clinic Studies and laboratory staff of Histopathology for their assistance.

CONFLICT OF INTEREST

The authors declared that they have no conflict of interest.

REFERENCES

Abdullah, F.F.J., Latif, N.AA., Chung, E.L.T., Aimi, S., Sarah, M.Z.S., Haron, A.W., Norsidin, M.J., 2015. Changes in the Reproductive Hormones of Non-Pregnant Does Infected Intradermally with *Corynebacterium pseudotuberculosis* in Chronic Form. Intl. J. Liv. Res. 5, 33-40.

Abdullah, F.F.J., Osman, A.Y., Adamu, L., Zakaria, Z., Abdullah, R., Saad, M.Z. Saharee, A. A., 2013. Acute phase protein profiles in calves following infection with whole cell, lipopolysaccharides, and outer membrane protein extracted from Pasteurella multocida type B: 2. A. J. Anim. Vet. Adv. 8, 655-662.

Abra, R., Quinn, P., 1975. A novel pathway for phosphatidylcholine catabolism in rat brain homogenates. Biochem. et Biophy. Acta. – Lip. and Lip. Met. 380, 436-441.

Adza-Rina, N., Nordi, M., Saad, M.Z., Abdullah, F.F.J., Saharee, A.A., Haron, A.W., Shamsudin, S., 2013. Clinical and pathological changes in goats inoculated *Corynebacterium pseudotuberculosis* by intradermal, intranasal and oral routes. Onl. J. Vet. Res. 17, 73-83.

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. S. Rum. Res. 94, 117-124.

Alshamaony, L., Goodfellow, M., Minnikin, D., Bowden, G., Hardie, J., 1977. Fatty and mycolic acid composition of Bacterionema matruchotii and related organisms. Microb. 98, 205-213.

Asselineau, C., Tocanne, G., Tocanne, J., 1970. Stéréochimie des acides mycoliques. Bull. Soc Chim. Fr., 1455.

Asselineau, J., Lederer, E., 1950. Structure of the mycolic acids of Mycobacteria. Nat. 166, 782-783.

Augustine, J.L., Renshaw, H., 1986. Survival of *Corynebacterium pseudotuberculosis* in axenic purulent exudate on common barnyard fomites. Ame. J. V. Res. 47, 713-715.

Ayers, J., 1977. Caseous lymphadenitis in goats and sheep: a review of diagnosis, pathogenesis, and immunity. J Ame. Vet. Med. Assoc. 171, 1251.

Baird, G., 2003. Current perspectives on caseous lymphadenitis. In Prac. 25, 62-68.

Baird, G., Fontaine, M., 2007. *Corynebacterium pseudotuberculosis* and its role in ovine caseous lymphadenitis. J. Comp. Path. 137, 179-210.

Barak ,V., Yanai, P., Treves, A.J., Roisman, I., Simon, A., Laufer, N., 1992. Interleukin-1: local production and modulation of human granulosa luteal cells steroidogenesis. Fert. Ster. 58, 719-725.

Barksdale, L., Linder, R., Sulea, I.T., Pollice, M., 1981. Phospholipase D activity of *Corynebacterium pseudotuberculosis* (*Corynebacterium ovis*) and *Corynebacterium ulcerans*, a distinctive marker within the genus *Corynebacterium*. J. Clin. Micro. 13, 335-343.

Barry, C.E., Lee, R.E., Mdluli, K., Sampson, A.E., Schroeder, B.G., Slayden, R.A., Yuan, Y., 1998. Mycolic acids: structure, biosynthesis and physiological functions. Prog. Lip. Res. 37, 143-179.

Bastos, B. L., Portela, R. D., Dorella, F. A., Ribeiro, D., Seyffert, N., Castro, T. L. D. P., Azevedo, V. (2012). *Corynebacterium pseudotuberculosis*: immunological responses in animal models and zoonotic potential. J. Clin. Cell Immunol. 4, 005.

Batey, R., 1986a. Pathogenesis of caseous lymphadenitis in sheep and goats. Aust. Vet. J. 63, 269-272.

Batey, R., Speed, C., Kobes, C., 1986b. Prevalence and distribution of caseous lymphadenitis in feral goats. Aust. Vet. J. 63, 33-36.

Bhatt, A., Molle, V., Besra, G.S., Jacobs, W.R., Kremer, L., 2007. The *Mycobacterium tuberculosis* FAS-II condensing enzymes: their role in mycolic acid biosynthesis, acid-fastness, pathogenesis and in future drug development. Mol. Microb. 64, 1442-1454.

Biberstein, E., Knight, H., Jang, S., 1971. Two biotypes of *Corynebacterium pseudotuberculosis*. Vet. Rec. 89, 691-692.

Braga, W., Schul S, Nunez A, Pezo D and Franco E 2007. A primary *Corynebacterium pseudotuberculosis* low dose infection in alpacas (Lama pacos) protects against a lethal challenge exposure. Small Rum Res. 72, 81-86.

Brogden, K., Cutlip, R., Lehmkuh, H., 1984. Experimental *Corynebacterium pseudotuberculosis* infection in lambs. Ame. J. Vet. Res. 45, 1532-1534.

Brown, C., Olander, H., 1987. Caseous lymphadenitis of goats and sheep: a review. Vet. Bull. 57, 112-11.

Brown, C., Olander, H., Biberstein, E., Morse, S., 1986. Use of a toxoid vaccine to protect goats against intradermal challenge exposure to *Corynebacterium pseudotuberculosis*. Ame. J. Vet. Res. 47, 1116-1119.

Brown, C.C., Olander, H.J., Alves, S.F., 1987. Synergistic hemolysis-inhibition titers associated with caseous lymphadenitis in a slaughterhouse survey of goats and sheep in Northeastern Brazil. Cand. J. Vet. Res. 51, 46.

Burkovski, A, 2018. The role of corynomycolic acids in *Corynebacterium*-host interaction. Anton. van Leeu. 111, 717-725.

Burkovski, A., 2013. Cell envelope of corynebacteria: structure and influence on pathogenicity. Intl. Schl. Res. Not. 2013.

Butler, W., Ahearn, D., Kilburn, J. 1986. High-performance liquid chromatography of mycolic acids as a tool in the identification of *Corynebacterium*, *Nocardia*, *Rhodococcus*, and *Mycobacterium* species. J. Clin. Microb. 23, 182-185.

Butler, W.R., Floyd, M.M., Brown, J.M., Toney, S.R., Daneshvar, M.I., Cooksey, R.C., Charles, N., 2005. Novel mycolic acid-containing bacteria in the family Segniliparaceae fam. nov., including the genus Segniliparus gen. nov., with descriptions of Segniliparus rotundus sp. nov. and Segniliparus rugosus sp. nov. Intl. J. Syst. Evol. Microb. 55, 1615-1624.

Butler, W.R., Guthertz, L.S., 2001. Mycolic acid analysis by high-performance liquid chromatography for identification of *Mycobacterium* species. Clin. Microb. Rev. 14, 704-726.

Cameron, S.P., Dunstan, S.J., Tachedjian, M., Krywult, J., Hodgson, A.L., Strugnell, R.A., 1998. Vaccine potential of attenuated mutants of *Corynebacterium pseudotuberculosis* in sheep. Infect. Immun. 66, 474-479.

Carne, H., 1939. A bacteriological study of 134 strains of *Corynebacterium ovis*. J. Pathol. Bact. 49, 313-328.

Carrington, C.B., Addington, W.W., Goff, A.M., Madoff, I.M., Marks, A., Schwaber, J.R, Gaensler, E.A., 1969. Chronic eosinophilic pneumonia. N. Engl. J. Med. 280, 787-798.

Catherine, S.J., 1994. Characterization of equine neutrophil surface antigens with an anti-β-integrin-like and two anti-CD18 monoclonal antibodies and effect of lipopolysaccharide stimulation. Doctoral dissertation, Virginia Tech.

Chaplin, P.J., De Rose, R., Boyle, J.S., McWaters, P., Kelly, J., Tennent, J.M., Scheerlinck, J.P.Y., 1999. Targeting improves the efficacy of a DNA vaccine against *Corynebacterium pseudotuberculosis* in sheep. Infec. Immun. 67, 6434-6438.

Collet, J.P., Burtin, P., Bossard, N., Ducruet, T., Kramer, M., Floret, D., 1994. Type of day-care setting and risk of repeated infections. Ped. 94, 997-999.

Collins, M.D., Burton, R.A., Jones, D., 1988. *Corynebacterium amycolatum*

spp. nov. a new mycolic acid-less *Corynebacterium* species from human skin. FEMS Microb. Lett. 49, 349-352.

Collins. M., Goodfellow, M., Minnikin, D., 1982. A survey of the structures of mycolic acids in *Corynebacterium* and related taxa. Microb. 128, 129-149.

Connor, K.M., Fontaine, M.C., Rudge, K., Baird, G.J. Donachie, W., 2007. Molecular genotyping of multinational ovine and caprine *Corynebacterium pseudotuberculosis* isolates using pulsed-field gel electrophoresis. Vet. Res. 38, 613-623.

Connor, K.M., Quirie, M.M., Baird, G., Donachie, W., 2000. Characterization of United Kingdom Isolates of *Corynebacterium pseudotuberculosis* Using Pulsed-Field Gel Electrophoresis. J. Clin. Microb. 38, 2633-2637.

Corbeil, L. B., 2016. Histophilus somni surface proteins. Hist. Som. 396, 89-107.

Costa, L.R., Spier, S.J., Hirsh, D.C., 1998. Comparative molecular characterization of *Corynebacterium pseudotuberculosis* of different origin. Vet. Microb. 62, 135-143.

Daffé, M., Draper, P., 1997. The envelope layers of mycobacteria with reference to their pathogenicity. Adv. Microb. Physiol. 39, 131-203.

Daffe, M., Laneelle, M., Asselineau, C., Levy-Frebault, V., David, H., 1983. Taxonomic value of mycobacterial fatty acids: proposal for a method of analysis. Ann. Microbiol. (Paris)134B, 241-256.

Damien, P., de Sousa-D'Auria, C., Houssin, C., Grimaldi, C., Chami, M., Daffé, M., Guilhot, C., 2004. A polyketide synthase catalyzes the last condensation step of mycolic acid biosynthesis in mycobacteria and related organisms. Proc. Nat. Acad. Sci. 101, 314-319.

De Rose, R., Tennent, J., McWaters, P., Chaplin, P.J., Wood, P.R., Kimpton, W., Scheerlinck, J.P.Y., 2002. Efficacy of DNA vaccination by different routes of immunisation in sheep. Vet. Immun. Immunopathol. 90, 55-63.

de Sá Guimarães, A., do Carmo, F.B., Pauletti, R.B., Seyffert, N., Ribeiro, D., Lage, A.P., Gouveia, A.M.G., 2011. Caseous lymphadenitis: epidemiology, diagnosis, and control. IIOAB J. 2, 33-43.

Dorella, F., Fachin, M., Billault, A., Neto, E.D., Soravito, C., Oliveira, S., Azevedo, V., 2006a. Construction and partial characterization of a *Corynebacterium pseudotuberculosis* bacterial artificial chromosome library through genomic survey sequencing. Gen. Mol. Res. 5, 653-663.

Dorella, F.A., Pacheco, L.G., Oliveira, S.C., Miyoshi, A., Azevedo, V., 2006b. *Corynebacterium pseudotuberculosis*: microbiology, biochemical properties, pathogenesis and molecular studies of virulence. Vet. Res. 37, 201-218.

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. Rev. Vacc. 8, 205-213.

Dubnau, E., Chan, J., Raynaud, C., Mohan, V.P., Lanéelle, M.A., Yu, K., Daffé, M., 2000. Oxygenated mycolic acids are necessary for virulence of *Mycobacterium tuberculosis* in mice. Mol. Microb. 36, 630-637.

Edwards, D.P., 2005. Regulation of signal transduction pathways by estrogen and progesterone. Annu. Rev. Physiol. 67, 335-376.

Egen, N., Cuevas, W., McNamara, P., Sammons, D., Humphreys, R., and Songer, J.G. 1989. Purification of the phospholipase D of *Corynebacterium pseudotuberculosis* by recycling isoelectric focusing. Ame. J. Vet. Res. 50, 1319-1322.

Eggleton, D., Middleton, H., Doidge, C., Minty, D., 1991. Immunisation against ovine caseous lymphadenitis: comparison of *Corynebacterium pseudotuberculosis* vaccines with and without bacterial cells. Aust. Vet. J. 68, 317-319.

El-Enbaawy, M.I., Saad, M.M., Selim., S.A., 2005. Humoral and cellular immune responses of a murine model against *Corynebacterium pseudotuberculosis* antigens. Infect. Immun. 12, 13-19.

Euzéby, J., 2003. List of Bacterial names with Standing in Nomenclature-Societé de Bactériologie Systématique et Vétérinaire-France. URL: http://www. bacterio. cict. fr). Acesso em, 20.

Euzéby, J.E., Spier, S.J., Mihalyi, J., Drazenovich, N., Leutenegger, C.M., 2004. Molecular epidemiologic features of *Corynebacterium pseudotuberculosis* isolated from horses. Ame. J. Vet. Res. 65, 1734-1737.

Faeza, N., Jesse, F., Hambali, I., Yusuf, A., Odhah, M., Wessam, M., Zamri, M., 2019b. Clinico-pathological responses in reproductive system and its associated lymph nodes of bucks challenged with *Corynebacterium pseudotuberculosis* and its mycolic acid extract. Comp. Clin. Pathol. 28, 1547-1558.

Faeza, N., Jesse, F.F.A., Hambali, I., Odhah, M., Umer, M., Wessam, M., Haron, A.W., 2019a. Responses of testosterone hormone concentration, semen quality, and its related pro-inflammatory cytokines in bucks following *Corynebacterium pseudotuberculosis* and its mycolic acid infection. Trop. Anim. Hlth. Prod. 51, 1855-1866.

Fontaine, M., Baird, G., 2008. Caseous lymphadenitis. Small Rum. Res. 76, 42-48.

Fraser, G. 1961. Haemolytic activity of *Corynebacterium ovis*. Nat. 189, 246.

González, F.H., Hernández, F., Madrid, J., Martínez-Subiela, S., Tvarijonaviciute, A., Cerón, J.J., Tecles, F., 2011. Acute phase proteins in experimentally induced pregnancy toxemia in goats. J. Vet. Diag. Invest. 23, 57-62.

Goodfellow, M., Weaver, C., Minnikin, D., 1982. Numerical classification of some *rhodococci*, *corynebacteria* and related organisms. Microb. 128, 731-745.

Gotoh, K., Mitsuyama, M., Imaizumi, S., Kawamura, I., Yano, I., 1991. Mycolic Acid-Containing Glycolipid as a Possible Virulence Factor of *Rhodococcus equi* for Mice. Microb. Immun. 35, 175-185.

Guimarães, A., Seyffert, N., Bastos, B., Portela, R., Meyer, R., Carmo, F., Heinemann, M., 2009. Caseous lymphadenitis in sheep flocks of the state of Minas Gerais, Brazil: prevalence and management surveys. S. Rum. Res. 87, 86-91.

Hard, G., 1972. Examination by electron microscopy of the interaction between peritoneal phagocytes and *Corynebacterium ovis*. J. Med. Microb. 5, 483-491.

Hard, G.C., 1975. Comparative toxic effect of the surface lipid of *Corynebacterium ovis* on peritoneal macrophages. Infec. Immun. 12, 1439-1449.

Henderson, A., 1979. Pseudotuberculous adenitis caused by *Corynebacterium pseudotuberculosis*. J. Med. Microb. 12, 147-150.

Hodgson, A., Krywult, J., Corner, L., Rothel, J., Radford, A., 1992. Rational attenuation of *Corynebacterium pseudotuberculosis* potential cheesy gland vaccine and live delivery vehicle. Infec. Immun. 60, 2900-2905.

Hong, S., Cheng., T.Y., Layre, E., Sweet, L., Young, D.C., Posey, J.E., Moody, D.B., 2012. Ultralong C100 mycolic acids support the assignment of Segniliparus as a new bacterial genus. PlOS one, 7, e39017.

Ibtisam, M.A., 2008 Some clinicopathological and pathological studies of *C. ovis* infection in sheep. Egypt. J. Comp. Pathol. Clin. Pathol. 21, 327-343.

Ingman, W.V., Jones, R.L., 2008. Cytokine knockouts in reproduction: the use of gene ablation to dissect roles of cytokines in reproductive biology. Hum. Rep. Upd. 14, 179-192.

Ioneda, T., 1989. Separation of homologues of methyl ester and 3-O-acetyl methyl ester derivatives of the corynomycolic acid fraction from *Corynebacterium pseudotuberculosis*. J. Chromat. A. 481, 411-415.

Ioneda, T., Silva, C.L., 1979. Purification of 1-monoacylglycerols containing α-branched-β-hydroxylated fatty acids from lipids of *Corynebacterium pseudotuberculosis*. Chem. Phys. Lip. 25, 85-91.

Irwin, M.R., Knight, H.D., 1975. Enhanced resistance to *Corynebacterium pseudotuberculosis* infections associated with reduced serum immunoglobulin levels in levamisole-treated mice. Infec. Immun. 12, 1098-1103.

James, D.G., Zumla, A., 1999. The granulomatous disorders. Cambr Uni Press.

Jeber, Z., MohdJin, Z., Jesse, F.F.A., Saharee, A., Sabri, J., Yusoff, R., Wahid, H., 2016. Influence of *Corynebacterium pseudotuberculosis* infection on level of acute phase proteins in goats. BMC Vet. Res. 12, 48.

Jesse, F.F.A., Ibrahim, H.H., Abba, Y., Chung, E.L.T., Marza, A.D., Mazlan, M. Mod-Lila, M.A., 2017a. Reproductive hormonal variations and adenohypophyseal lesions in pre-pubertal buffalo heifers inoculated with Pasteurella multocida type B: 2 and its immunogens. BMC Vet. Res. 13, 88.

Jesse, F.F.A., Latif, N.A.A., Chung, E.L.T., Adamu, L., Sarah, S. A., Zamri-Saad, M., Mohd M.A., 2016. Cytokines (IL 1β and IL 6) Responses in Non-Pregnant Does Infected with *Corynebacterium pseudotuberculosis* Following Intradermal Route of Infection in Chronic State. Intl. J. Liv. Res. 6, 1-8.

Jesse, F.F.A., Odhah, M.N., Abba, Y., Garba, B., Mahmood, Z., Hambali, I.U., Zamri-Saad, M., 2020. Responses of female reproductive hormones and histopathology in the reproductive organs and associated lymph nodes of Boer does challenged with *Corynebacterium pseudotuberculosis* and its immunogenic corynomycolic acid extract. Microb. Pathol. 139, 103852.

Jesse, F.F.A., Odhah, M.N., Mohd-Lila, M.A., Saad, M.Z., Haron, A.W., Hambali, I.U., Mahmood, Z.K., 2017b. Pro-Inflammatory Cytokine (IL-1β and IL-6) Response in Goats Challenged with *Corynebacterium pseudotuberculosis* and its Immunogen Mycolic Acids. Ame. J. Anim. Vet. Sci. 12, 26-31.

Jesse, F.F.A., Sang, S.L., Saharee, A.A., Shahirudin, S., 2011. Pathological changes in the organs of mice model inoculated with *Corynebacterium pseudotuberculosis* organism. Pert. J. Trop. Agri. Sci. 34, 145-149.

Jesse, F.FA., Azlan, C., Saharee, A., Murugaiyah, M., Noordin, M., Jasni, S., Siti, K., 2008. Control of Caseous Lymphadenitis (CLA) in goat at UPM Farm. Proceedings: 20th Vet Asso Mala (VAM).

Jesse. F.F.A., Randolf, P., Saharee, A., Haron, A.W., Zamri-Saad, M., Jasni, S., Abdinasir, Y., 2013a. Clinico-pathological response of mice following oral route infection of *C. pseudotuberculosis*. J. Agric. Vet. Sci. 2, 38-42.

Jolly, R., 1965. The pathogenesis of experimental *Corynebacterium ovis*

infection in mice. N. Zel.Vet. J. 13, 141-147.
Khuder, Z., Osman, A.Y., Jesse, F.F., Wahid, A., Saharee, A.A., Jasni, S., Rasedee, A., 2012. Sex hormone profiles and cellular changes of reproductive organs of mice experimentally infected with *Corynebacterium pseudotuberculosis* and its exotoxin phospholipase D. J. Agri. Vet. Sci. 1, 24-29.
Kim, Y.J., Kim, H.J., Jeong, S.K., Lee, S.H., Kang, M.J., Yu, H.S., Yu, J., 2014. A novel synthetic mycolic acid inhibits bronchial hyperresponsiveness and allergic inflammation in a mouse model of asthma. Aller. Asth. Immunol. Res. 6, 83-88.
Komala, T., Ramlan, M., Yeoh, N., Surayani, A., Sharifah, H. S., 2008. A survey of caseous lymphadenitis in small ruminant farms from two districts in Perak, Malaysia-Kinta and Hilir Perak. Trop. Biomed. 25, 196-201.
Korf, J.E., Pynaert, G., Tournoy, K., Boonefaes, T., Van Oosterhout, A., Ginneberge, D., Grooten, J., 2006. Macrophage reprogramming by mycolic acid promotes a tolerogenic response in experimental asthma. Ame. J. Resp. Crit. Care Med. 174, 152-160.
Lan, D.T., Makino, S., Shirahata, T., Yamada, M., Nakane, A., 1999. Tumor necrosis factor alpha and gamma interferon are required for the development of protective immunity to secondary *Corynebacterium pseudotuberculosis* infection in mice. J. Vet. Med. Sci. 61, 1203-1208.
Laneelle, M.A., Eynard, N., Spina, L., Lemassu, A., Laval, F., Huc, E., Daffé, M., 2013. Structural elucidation and genomic scrutiny of the C60–C100 mycolic acids of Segniliparus rotundus. Microb. 159, 191-203.
Latif, N.A.A., Abba, Y., Jesse, F.F.A., Chung, E.L.T., Zamri-Saad, M., Saharee, A.A., Mohd-Lila, M.A., 2017. Histopathological assessment of chronic *Corynebacterium pseudotuberculosis* infection in the reproductive tract and iliac lymph node of Katjang does. Comp. Clin. Pathol. 26, 147-154.
Latif, N.A.A., Abdullah, F.F.J., Othman, A.M., Rina, A., Chung, E.L.T., Zamri-Saad, M., Mohd-Lila, M.A., 2015. Isolation and detection of *Corynebacterium pseudotuberculosis* in the reproductive organs and associated lymph nodes of non-pregnant does experimentally inoculated through intradermal route in chronic form. Vet. Wld. 8, 924.
Laval, F., Lanéelle, M.A., Déon, C., Monsarrat, B., Daffé, M., 2001. Accurate molecular mass determination of mycolic acids by MALDI-TOF mass spectrometry. Anal. Chem. 73, 4537-4544.
Mahmood, Z., Jesse, F.F.A., Saharee, A., Jasni, S., Yusoff, R., Wahid, H., 2015a. Assessment of blood changes post-challenge with *Corynebacterium pseudotuberculosis* and its exotoxin (phospholipase D): A comprehensive study in goat. Vet. Wld. 8, 1105.
Mahmood, Z., Jesse, F.F.A., Saharee, A., Jasni, S., Yusoff, R., Wahid, H., 2015b. Clinio-pathological changes in goats challenged with *Corynebacterium* Peudotuberculosis and its exotoxin (PLD). Ame. J. Anim. Vet. Sci. 10, 112-132.
Mahmood, Z.K., Jin, Z.A.M., Jesse, F.F., Saharee, A.A., Sabri, J., Yusoff, R., Haron, A.W., 2016. Relationship between the *Corynebacterium pseudotuberculosis*, phospholipase D inoculation and the fertility characteristics of crossbred Boer bucks. Lives. Sci. 191, 12-21.
Marrakchi, H., Lanéelle, M.A., Daffé, M., 2014. Mycolic acids: structures, biosynthesis, and beyond. Chem. Biol. 21, 67-85.
McKean, S.C., Davies, J.K., Moore, R.J., 2007. Expression of phospholipase D, the major virulence factor of *Corynebacterium pseudotuberculosis*, is regulated by multiple environmental factors and plays a role in macrophage death. Microb. 153, 2203-2211.
McNamara, P.J., Bradley, G.A., Songer, J.G., 1994. Targeted mutagenesis of the phospholipase D gene results in decreased virulence of *Corynebacterium pseudotuberculosis*. Mol. Microb. 12, 921-930.
McNeil, M., Daffe, M., Brennan, P., 1991. Location of the mycolyl ester substituents in the cell walls of mycobacteria. J. Biol. Chem. 266, 13217-13223.
Minnikin, D., Minnikin, S., Dobson, G., Goodfellow, M., Portaels, F., Van Den Breen, L., Sesardic, D., 1983. Mycolic acid patterns of four vaccine strains of *Mycobacterium bovis* BCG. Microb. 129, 889-891.
Moura-Costa, L., Bahia, R., Carminati, R., Vale, V., Paule, B., Portela, R., Barreto, L., 2008. Evaluation of the humoral and cellular immune response to different antigens of *Corynebacterium pseudotuberculosis* in Canindé goats and their potential protection against caseous lymphadenitis. Vet. Immun. Immunopathol. 126, 131-141.
Muckle, C.A., Gyles, C., 1983. Relation of lipid content and exotoxin production to virulence of *Corynebacterium pseudotuberculosis* in mice. Ame. J. Vet. Res. 44, 1149-1153.
Muckle, C.A., Menzies, P.I., Li, Y., Hwang, Y.T., van Wesenbeeck, M., 1992. Analysis of the immunodominant antigens of *Corynebacterium pseudotuberculosis*. Vet. Microb. 30, 47-58.
Nieto, N.C., Foley, J.E., MacLachlan, N.J., Yuan, T., Spier, S.J., 2009. Evaluation of hepatic disease in mice following intradermal inoculation with *Corynebacterium pseudotuberculosis*. Ame. J. Vet. Res. 70, 257-262.
Odhah, M., Jesse, F., Lawan, A., Hambali, I.U., Marza, A., Mahmood, Z., Mohd-Azmi, M.L., 2018. Responses of haptoglobin and serum amyloid A in goats inoculated intradermally with *C. pseudotuberculosis* and mycolic acid extract immunogen. Microb. Pathogen. 117, 243-246.
Odhah, M.N., Abdullah. F.F.J., Haron, A.W., Mohd-Lila, M.A., Zamri-Saad, M., Khuder, Z., and Saleh, W.M., 2017. Hemogram responses in goats toward challenged with *Corynebacterium pseudotuberculosis* and its immunogen mycolic acids. Vet. Wld. 10, 655-661.
Odhah, M.N., Jesse, F.F.A., Chung, E.L.T., Mahmood, Z., Mohd-Lila, M.A., Zamri-Saad, M., 2019. Clinico-pathological responses and PCR detection of *Corynebacterium pseudotuberculosis* and its immunogenic mycolic acid extract in the vital organs of goats. Microb. Pathogen. 135, 103628
Oliveira, A., Oliveira, L.C., Aburjaile, F., Benevides, L., Tiwari, S., Jamal, S.B., Portela, R.W., 2017. Insight of genus *Corynebacterium*: ascertaining the role of pathogenic and non-pathogenic species. Front. Microb. 8, 1937.
Onon, E. O., 1979. Purification and partial characterization of the exotoxin of *Corynebacterium ovis*. Biochem. J. 177, 181-186.
Osman, A.Y., Abdullah, F.F.J., Saharee, A.A., Sabri, J., Bejo, S.K., Haron, A.W., 2012b. Acute phase response in mice experimentally infected with whole cell and exotoxin (PLD) extracted from *Corynebacterium pseudotuberculosis*. J. Anim. Vet. Advan. 11, 4008-4012.
Osman, A.Y., Abdullah. F.F.J., Saharee, A.A., Haron, A.W., Sabri, I., Abdullah, R., 2012a. Haematological and Biochemical Alterations in Mice Following Experimental Infection with Whole Cell and Exotoxin (PLD) Extracted from *C. pseudotuberculosis*. J. Anim. Vet. Advan. 11, 4660-4667.
Othman, A. M., Abdullah, F.F.J., Nordi, M., Rina, N.A., Ilyasu, Y., Mohd-Lila, M.A., 2014a. Haemotological, biochemical and serum electrolyte changes in non-pregnant boer does inoculated with *Corynebacterium pseudotuberculosis* via various routes. IOSR J. Agri. Vet. Sci. 7, 5-8.
Othman, A.M., Jesse, F., Adza-Rina, M., Ilyasu, Y., Zamri-Saad, M., Haron, A.W., Mohd-Lila, M.A., 2014b. Responses of inflammatory cytokines in non-pregnant Boer does inoculated with *Corynebacterium pseudotuberculosis* via various routes. Res. Opin. Anim. Vet. Sci. 4.
Othman, A.M., Jesse, F.F.A., Adamu, L., Abba, Y., Adza Rina, M., Saharee, A.A., Zamri-Saad, M., 2014c. Changes in serum progesterone and estrogen concentrations in non-pregnant boer does following experimental infection with *Corynebacterium pseudotuberculosis*. J. Vet. Adv. 4, 524-528.
Papaioannou, N., Zavlaris, M., Giadinis, N., Petridou, E., Psychas, V., 2010. Case report: A case of kidney infection by *Corynebacterium pseudotuberculosis* in sheep. J. Hell. Vet. Med. Soc. 61, 29-35.
Paton, M., Walker, S., Rose, I., Watt, G., 2003. Prevalence of caseous lymphadenitis and usage of caseous lymphadenitis vaccines in sheep flocks. Aust. Vet. J. 81, 91-95.
Paton, M.W., 2010. The epidemiology and control of caseous lymphadenitis in Australian sheep flocks. (Doctoral dissertation, Murdoch University).
Pawełczyk, J., Kremer, L., 2014. The molecular genetics of mycolic acid biosynthesis. Mol. Gen. Mycobac. 611-631.
Pazatsen Randolf Sam Shun, Faez Firdaus Jesse Abdullah, Mohd Zamri Saad, Haron, A. W., 2012. Clinical response and pathological changes associated with *Corynebacterium pseudotuberculosis* infection in mice. Paper presented at the 7th Proceedings of the Seminar in Veterinary Sciences.
Pepin, M., Fontaine, J.J., Pardon, P., Marly, J., Parodi, A., 1991a. Histopathology of the early phase during experimental *Corynebacterium pseudotuberculosis* infection in lambs. Vet. Microb. 29, 123-134.
Pepin, M., Pardon, P., Lantier, F., Marly, J., Levieux, D., Lamand, M., 1991b. Experimental *Corynebacterium pseudotuberculosis* infection in lambs: kinetics of bacterial dissemination and inflammation. Vet. Microb. 26, 381-392.
Pepin, M., Pittet, J., Olivier, M., Gohin, I., 1994. Cellular composition of *Corynebacterium pseudotuberculosis* pyogranulomas in sheep. J. Leuk. Biol. 56, 666-670.
Perkins, S.L., Magdesian, K.G., Thomas, W.P., Spier, S.J., 2004. Pericarditis and pleuritis caused by *Corynebacterium pseudotuberculosis* in a horse. J. Ame. Vet. Med. Assoc. 224, 1133-1138.
Peyron, P., Vaubourgeix, J., Poquet, Y., Levillain, F., Botanch, C., Bardou, F., Cardona, P.J., 2008. Foamy macrophages from tuberculous patients' granulomas constitute a nutrient-rich reservoir for *M. tuberculosis* persistence. PLoS Pathog. 4, e1000204.
Pinho, J., Dorella, F., Coelho, S., Fonseca, C., Cardoso, F., Meyer, R., 2009. Heat-shock protein (Hsp)-60 is able to induce an immune response in mice, but fails to confer protection against infection. Open Vet. Sci. J. 3, 22-27.
Portevin, D., de Sousa-D'Auria, C., Houssin, C., Grimaldi, C., Chami, M., Daffé, M., Guilhot, C., 2004. A polyketide synthase catalyzes the last

condensation step of mycolic acid biosynthesis in mycobacteria and related organisms. Proc. Nat. Acad. Sci. 101, 314-319.

Portevin, D., de Sousa-D'Auria, C., Montrozier, H., Houssin, C., Stella, A., Lanéelle, M.A., Daffé, M., 2005. The Acyl-AMP Ligase FadD32 and AccD4-containing Acyl-CoA Carboxylase Are Required for the Synthesis of Mycolic Acids and Essential for Mycobacterial Growth Identification of the Carboxylation Product And Determination of The Acyl-Coa Carboxylase Components. J. Biol. Chem. 280, 8862-8874.

Ribeiro, D., Dorella, F.A., Pacheco, L.G.C., Seyffert, N., Castro, T.L.D.P., Portela, R.W.D., Azevedo, V., 2013. Subclinical diagnosis of Caseous lymphadenitis based on Elisa in Sheep from Brazil. J. Bact. Parasit. 1-4.

Roberson, J.R., Baird, A.N., Pugh, D.G., 2012. Diseases of the integumentary system. Sheep and Goat Medicine. 2nd ed. Eds Pugh. D. G, Baird. AN Maryland Heights, Mo: Saunders Elsev. 256-290.

Simmons, C.P., Hodgson, A., Strugnell, R.A., 1997. Attenuation and vaccine potential of aroQ mutants of *Corynebacterium pseudotuberculosis*. Infec. Immun. 65, 3048-3056.

Sirotkin, A.V., 2011. Cytokines: signalling molecules controlling ovarian functions. Itl. J. Biochem. Cell Biol. 43, 857-861.

Skinner, E.A., 1991. Development and perceived control: A dynamic model of action in context.

Songer, J.G., 1997. Bacterial phospholipases and their role in virulence. Trend. Microb. 5, 156-161.

Songer, J.G., Beckenbach, K., Marshall, M.M., Olson, G.B., Kelley, L., 1988. Biochemical and genetic characterization of *Corynebacterium pseudotuberculosis*. Ame. J. Vet. Res. 49, 223-226.

Stackebrandt, E., Rainey, F.A., Ward-Rainey, N.L., 1997. Proposal for a new hierarchic classification system, Actinobacteria classis nov. Intl. J. Syst. Evol. Microb. 47, 479-491.

Stanford, K., Brogden, K., McClelland, L., Kozub, G., Audibert, F., 1998. The incidence of caseous lymphadenitis in Alberta sheep and assessment of impact by vaccination with commercial and experimental vaccines. Canad. J. Vet. Res. 62, 38.

Stefánska, I., Gierynska, M., Rzewuska, M., Binek, M., 2010. Survival of *Corynebacterium pseudotuberculosis* within macrophages and induction of phagocytes death. Pol. J. Vet. Sci. 13, 143.

Stoops, S.R.H., Thilsted, J., 1984. Ovine caseous lymphadenitis: disease prevalence, lesion distribution, and thoracic manifestations in a population of mature culled sheep from western United States. Ame. J. Vet. Res. 45, 557-561.

Sutherland, S., Hart, R., Buller, N., 1996. Genetic differences between nitrate-negative and nitrate-positive *C. pseudotuberculosis* strains using restriction fragment length polymorphisms. Vet. Microb. 49, 1-9.

Tashijian, J., Campbell, S., 1983. Interaction between caprine macrophages and *Corynebacterium pseudotuberculosis* an electron microscopic study. Ame. J. Vet. Res. 44, 690-693.

Timoney, J.F., Gillespie, J.H., Scott, F.W., Barlough, J.E., 1988. Hagan and Bruner's microbiology and infectious diseases of domestic animals: Cornell Uni Press.

Tomiasu, I., Yano, I., 1984. Separation and analysis of novel polyunsaturated mycolic acids from a psychrophilic, acid-fast bacterium, Gordona aurantiaca. Euro. J. Bioch. 139, 173-180.

Tothova, C., Nagy, O., Kovac, G., 2014. Acute phase proteins and their use in the diagnosis of diseases in ruminants: a review. Vet. Med. Czech. 59, 163-180.

Umer, M., Jesse, F.F.A., Saleh, W.M.M., Chung. E.L.T., Haron, A.W., Saharee, A.A., Sharif, A., 2020. Histopathological changes of reproductive organs of goats immunized with *Corynebacterium pseudotuberculosis* killed vaccine. Microb. Patho. 149, 104539.

Watanabe, D., Abe, M., Ohya, Y., 2001. Yeast Lrg1p acts as a specialized RhoGAP regulating 1, 3-β-glucan synthesis. Yeast, 18, 943-951.

Williamson, L.H., 2001. Caseous lymphadenitis in small ruminants. Vet. Clin. Nth Ame: F. Anim. Pract. 17, 359-371.

Yeruham, I., Braverman, Y., Shpigel, N., Chizov-Ginzburg, A., Saran, A., Winkler, M., 1996. Mastitis in Dairy Cattle Caused by *Corynebacterium pseudotuberculosis* and the Feasibility of Transmission by Houseflies I. Vet Quart. 18, 87-89.

Yozwiak, M., Songer, J.G., 1993. Effect of *Corynebacterium pseudotuberculosis* phospholipase D on viability and chemotactic responses of ovine neutrophils. Ame. J. Vet. Res. 54, 392.

Zaki, M., 1976. Relation between the toxogenicity and pyogenicity of *Corynebacterium ovis* in experimentally infected mice. Res. Vet. Sci. 20, 197-200.

Zuber, B., Chami, M., Houssin, C., Dubochet, J., Griffiths, G., Daffé, M., 2008. Direct visualization of the outer membrane of mycobacteria and corynebacteria in their native state. J. Bact. 190, 5672-5680.