



# A Review on the Potential Effects of *Mannheimia haemolytica* and its Immunogens on the Female Reproductive Physiology and Performance of Small Ruminants

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**Abstract** | *Mannheimia haemolytica* causes pneumonic pasteurellosis (mannheimiosis) in ruminants which is the most economically significant infectious disease. *Mannheimia* belongs to the family Pasteurellaceae, are nonmotile, non-spore-forming, facultatively anaerobic, oxidase-positive and fermentative gram-negative rods or coccobacilli which are frequent respiratory and digestive tract commensals in both domestic and wild animals. They can produce infection in animals with compromised immune states. The capsular polysaccharide, lipopolysaccharide and iron-regulated outer membrane proteins are the major virulent factors of organism stimulating the host immunity. There is a significant gap on the effects of the *M. haemolytica* and its immunogens on the physiology and performance of the reproductive system in small ruminants. Therefore, the goal of this review is to highlight the potential involvement of the female reproductive system with infection with *M. haemolytica* and its immunogens in small ruminants. Moreover, the review has directed the future research path to determine the role of this bacterium in the pathophysiology and performance of the female reproductive system.

**Keywords** | *Mannheimia haemolytica*, Pneumonic pasteurellosis, Immunogens, Reproductive physiology, Small ruminants

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## INTRODUCTION

*Mannheimia* (formerly known as *Pasteurella*) *haemolytica* is the causative agent of cattle and sheep pneumonic pasteurellosis (mannheimiosis), which is an infection that

causes significant financial losses to the cattle, sheep and goat sectors with climatic and animal management factors participating in their pathogenesis (Zamri-Saad et al., 1994; Chung et al., 2015; Jesse et al., 2019). *Pasteurella* and *Mannheimia* species are nonmotile, non-spore-forming,

facultatively anaerobic, oxidase-positive and fermentative small gram-negative rods or coccobacilli. Most of them are commensals on the upper respiratory mucous membrane and the digestive tract of both domestic and wild animals (Wilson and Ho, 2013). In its typical clinical form, the disease is enormously infectious, often fatal and has a very severe financial effect on the animal industry (Mohamed and Abdelsalam, 2008). The economic loss due to pneumonia in ruminants is estimated to be 8% of the total cost of production, that includes expenses in medical procedure, reduced food conversion, enhanced cost of production and reduced food supply for the people (Rico et al., 2017).

Infections from *Mannheimia* pathogens are correlated with poor management policies and develop as a secondary infection or as a result of acute stress. Transportation stress, viral infections, congested pens, inadequate housing conditions, abrupt improvements to the environment and other adverse situations improve the susceptibility of animals to *M. haemolytica* pneumonia (Abdullah et al., 2015; Jesse et al., 2017a). Moreover, *M. haemolytica* has many potential immunogens, including capsular polysaccharides, lipopolysaccharide (LPS), outer membrane proteins (OMPs), fimbriae, iron-regulated proteins and secreted leukotoxin (Confer, 1993).

Animals infected with pneumonia develop clinical signs including high fever, extreme respiratory involvements established by nasal discharges, frothy mouth, cough and dyspnoea (Mohamed and Abdelsalam, 2008). The diagnosis of pneumonic pasteurellosis is based on history of the clinical manifestation, clinical signs, post-mortem and histopathological results, associated with the isolation of the bacteria and confirmation with the use of PCR (Ahmed et al., 2017). Treatment can be achieved with a combination of antimicrobials such as penicillin, ampicillin, ceftriaxone and enrofloxacin and suitable anti-inflammatory agents like flunixin meglumine, meloxicam (Rahal et al., 2014; Thiry et al., 2014; Achard et al., 2018; Politis et al., 2019). However, prevention plans remain more efficient, which includes improving housing situations, sanitation and biosecurity procedures. It is best to avoid stressors, such as assembling animals of different backgrounds without adequate quarantine (Taunde et al., 2019).

The pathophysiology of the respiratory system due to *M. haemolytica* was focused in previous studies (Abdullah et al., 2015). However, it is unknown whether *M. haemolytica* have insidious effects on the reproductive system as it was often overlooked by the farmers and veterinarians. As far as we know, there is less information available on the reproductive physiology and pathological changes in small ruminants after infection of *M. haemolytica* and its immunogens. Therefore, the goal of this review is to

highlight the importance of *M. haemolytica* infection of female reproductive system in small ruminants to concentrate the researchers for further work on this neglected area.

## BIOLOGY OF *MANNHEIMIA HAEMOLYTICA*

### HISTORY AND TAXONOMY OF *MANNHEIMIA HAEMOLYTICA*

*Mannheimia haemolytica* is the most prevalent etiological agent of pneumonia in sheep, goats and other species of ruminants which cause economic losses worldwide due to high mortality, cost of treatment, poor weight gain and condition (Highlander, 2001). *M. haemolytica* formerly was known as *Pasteurella haemolytica*, which is involved in the aetiology of ovine pneumonia or enzootic pneumonia (Kumar et al., 2015) and bovine respiratory disease (BRD) (Confer, 2009), and it is in the family of Pasteurellaceae, genus Mannheimia (Rice et al., 2007).

There has been an extensive reclassification of the bacterium in the past; Theodore kit named it *bacterium bipolare multocidum* first in 1885, and ten years later Flugge renamed it *bacillus bovisseptica* in 1896 and subdivided it further into various types triggering bovine fibrinous pneumonia (*Pasteurella bovisseptica*) or hemorrhagic septicaemia (now known as *Pasteurella multocida*) (Highlander, 2001). Jones (1921) has reported three groups of bovine Pasteurella and stated that group I is different from other groups in its ability to hemolyze and its failure to produce indole. Further characterisation of strains was carried on by Newson and Cross (1932), and for group I of *Bacillus bovissepticus* they suggested the term *Pasteurella haemolytica*, as this group caused pneumonia in calves (Angen et al., 1999). Based on phenotypic epidemiological and pathological characters, Smith (1959) identified two biotypes of *P. haemolytica*. These biotypes were identified as A and T, corresponding to either L-arabinose or trehalose fermentation ability. Seventeen serotypes of *P. haemolytica* have been described, 13 identified as serotype A and four serotype T (Yunan and Fodor, 1995). Serotype T strains were subsequently reclassified as *Pasteurella trehalosi* and eventually *Bibersteinia trehalose* (Blackall et al., 2007). Serotype A strains of the old *P. haemolytica* with five species namely *Mannheimia haemolytica*, *Mannheimia glucosida*, *Mannheimia granulomatous*, *Mannheimia ruminalis* and *Mannheimia varigena* formed new genus called Mannheimia (Blackall et al., 2001; Angen et al., 2002; Ponnusamy et al., 2017).

*M. haemolytica* serotypes A1 and A2 are the common serotypes usually distributed all over the world. Serotype A1 is considered to be the most prevalent cause of bovine pasteurellosis, although certain serotypes, such as A6 and A9, are commonly correlated with bovine diseases (Quirie et al., 1986). While serotype A2 is the most common serotype related to the disease in sheep and goats; in healthy

calves, it is also a prevalent member of flora in the upper respiratory tract. Furthermore, *M. haemolytica* serotypes A1 and A2 that inhabit both cattle and sheep upper respiratory tracts are typically species-specific in their potential to induce lower respiratory disease (Highlander, 2001).

*M. haemolytica* serotype A1 as stated is the main reason of pneumonic pasteurellosis in cattle, and *M. haemolytica* serotypes A2 is also the leading cause of sheep and goats pneumonic pasteurellosis while serotypes of *B. trehalosi* cause the disease septicaemic pasteurellosis in sheep and goats, and interspecies serotypes transmission amid domestic ruminants, as well as between domestic and wild ruminants, has been stated (Berhe et al., 2017).

#### MORPHOLOGY OF *MANNHEIMIA HAEMOLYTICA*

Species of the genera *Pasteurella* and *Mannheimia* of the family Pasteurellaceae are small gram-negative rods or coccobacilli, nonmotile, non-spore-forming, facultatively anaerobic, oxidase-positive, and fermentative, and they naturally inhabit in the domestic and wild animals upper respiratory and digestive tract mucous membrane (Wilson and Ho, 2013). These organisms grow best on blood agar and produce a narrow zone of haemolysis, and they also grow on MacConkey agar (Tabatabaei and Abdollahi, 2018). Blood smears stained by Giemsa methods, pasteurellae species show bipolar staining, which is the characteristic staining pattern for these organisms (Ashraf et al., 2011).

#### PATHOGENESIS AND PATHOLOGY OF *MANNHEIMIA HAEMOLYTICA*

##### PATHOGENICITY OF *MANNHEIMIA HAEMOLYTICA*

*Mannheimia* species are common commensals of the nasopharynx in many domestic and wild animals, including cats, dogs, horses, birds, and ruminants (Adamu, 2007; Roier et al., 2013). These species can cause infection when the animals' immunity becomes compromised (Guzmán-Brambila et al., 2012; Assefa and Kelkay, 2018). Furthermore, *M. haemolytica* is the most significant bovine respiratory disease complex bacterial pathogen. It induces in its most serious type, severe fibrinous pleuropneumonia characterised by extensive leukocyte infiltration in alveoli, intraalveolar haemorrhage, deposition of fibrin, and consolidation of the lungs (Aulik et al., 2012).

Most species of animals are *M. haemolytica* and *P. trehalosi* asymptomatic carriers, and also they carry strains of *P. multocida*. In cattle, *M. haemolytica* is associated with diseases including pneumonic pasteurellosis, haemorrhagic septicaemia and abortion, mastitis, pneumonia, and septicaemia in domestic sheep and isolates in domestic goats (Adamu, 2007). A study by Williams et al. (2005) for evaluating the postpartum vaginal mucus clinically in cattle stated that *M. haemolytica* is linked with fetid vaginal mucus odour. Therefore, the authors have seen that there

was an increased risk for fetid vaginal mucus odour and culture growth of *M. haemolytica*. The involvement of *M. haemolytica* in vaginal mucus odour was a new observation. However, *M. haemolytica* effects on the reproductive system in small ruminants remains unclear, and its pathogenesis has to be discovered.

Transmission of *Pasteurella* is likely caused by inhalation of the contaminated droplet, coughed up or exhaled from infected animals which may be the clinical case or recovered carriers where the infection persists in the upper respiratory tract (Kabeta et al., 2015). *M. haemolytica* is carried in the nasopharynx and tonsils of seemingly healthy animals (Rowe et al., 2001). *P. multocida* and *M. haemolytica* are particularly vulnerable to the environmental influence, and the mediated contagion is uncertain to be an essential factor in the disease transmission. Under favourable circumstances, particularly when cattle are confined in inadequately ventilated trains, the disease will spread very rapidly in holding pens and feedlots, and affect a significant percentage of the herd within 48 hours. However, animals at pasture are able to move freely, which decreases the rate of spread (Kabeta et al., 2015).

#### VIRULENCE FACTORS

*M. haemolytica* has a number of potential immunogens. Capsular polysaccharide, LPS, OMPs, fimbriae, iron-regulated proteins and a secreted leukotoxin (LKT) are the most likely potential ones to stimulate immunity (Confer, 1993). These factors make it possible for *M. haemolytica* to cytolysise alveolar phagocytic cells and replicate in the lung that further increases proliferation of the bacteria and involvement of the direct or indirect role in lung injury (Jeyaseelan et al., 2002).

#### CAPSULE

The cell capsule plays a significant role in the pathogenicity of pathogenic bacteria and the growth of the infection. Virulence mechanism of the cell capsule is largely due to its potential to interfere host immune defence against invading organism (Chae et al., 1990). In addition to its antiphagocytic abilities, *M. haemolytica* cell capsule can serve as an adhesin (Confer, 2009). Each *M. haemolytica* serotype develops a characteristic polysaccharide capsule to avoid macrophages and polymorphonuclear leukocytes from phagocytosis and to prevent the organism from the complement-mediated destruction of the serum outer membrane (Mohamed and Abdelsalam, 2008). The capsular polysaccharide of *M. haemolytica* Serotype A1 is composed repeats of N-acetylmannosaminuronic acid and N-acetylmannosamine that is needed to promote adherence, inhibit neutrophils phagocytosis and assist the pathogen in avoiding immune system (Klima et al., 2017), whereas serotype A2 capsule consists of linear N-acetylneuraminic acid (Neu5Ac) polymer with  $\alpha$  (2–8) linkages of polysialic

acid (PolySia) that is identical to those found on the host cells (Klima et al., 2017; Lizak et al., 2017). The molecular mimicry of PolySia bacterial capsules is an effective method to prevent the host's immune detection, as they are not considered foreign (Mazmanian and Kasper, 2006). Capsular polysaccharide deposition in the sheep lungs results in oedema and a mild neutrophilic infiltration with capsular polysaccharide binding to surfactant (Confer and Ayalew, 2018).

*M. haemolytica* capsular material can also interfere with the pulmonary surfactant to facilitate the adherence of the invading organism to the susceptible animals in the epithelium of the respiratory tract (Brogdén et al., 1989). The capsular polysaccharide is immunogenic, but responses of antibody to capsular polysaccharide do not associate with resistance to experimental challenges (Confer, 2009).

### FIMBRIAE

Bacterial adhesins, such as fimbriae are the first factors interacting with the host in an infection process, suggesting that these factors are likely to have a vital impact on the ability of the bacteria to survive and subsequently colonise the host (Kline et al., 2009). For gram-negative bacteria, the importance of fimbriae virulence is due to their ability to attach host tissue as fimbrial antigens on bacterial surfaces are abundant in general and highly immunogenic (Rajeev et al., 2001). Two types of fimbriae have been found in *M. haemolytica* serotype 1; one is rigid and large, measures 12 nm in width, and the other one measures only 5 nm that is flexible and smaller in size (Morck et al., 1987; Potter et al., 1988). The two types of *M. haemolytica* fimbriae can enhance the organism mucosal attachment and colonisation of cattle and sheep lower respiratory tract epithelium (Mohamed and Abdelsalam, 2008).

### LIPOPOLYSACCHARIDE (LPS)

Basic *M. haemolytica* LPS composition has been reported to be close to that of other Gram-negative bacteria (Jeyaseelan et al., 2002). It was observed that *M. haemolytica* serotypes 2 and 8 to possess a rough LPS, whereas the remaining 14 serotypes have a distinctive smooth LPS (Lacroix et al., 1993). The LPS accounts for 10-25% of the dry weight of the bacteria *M. haemolytica* (Highlander, 2001; Leite et al., 2003). Moreover, LPS is an essential component of the Gram-negative bacterial cell wall outer membrane. LPS of *M. haemolytica* is made up of a lipid A, core oligosaccharide and polysaccharide side-chain that is called (O antigen) (Jeyaseelan et al., 2002).

Most of the effects caused by LPS are regulated by its lipid A component (Ulevitch and Tobias, 1995). The lipid A moiety participates in the anchoring of the LPS into the outer membrane, and it consists of phospholipids and lipids, meaning the lipid A unit known as endotoxin, with

the toxic and pyrogenic effects of LPS (Mamat et al., 2015). Besides, the immunogenicity of LPS O antigen and the cross-reactivity of antibodies between different serotypes, there is, unfortunately, no correlation between pneumonia development and high antibody response to LPS in terms of host protection (Confer et al., 1990). Therefore, LPS can lead to pulmonary pathology in a number of complex mechanisms, that includes direct pulmonary endothelium toxicity effects, activation of complement and subsequent recruitment of neutrophils (Gonzalez and Maheswaran, 1993; Leite et al., 2003).

LPS can also lead to the extent of lung lesions by bovine leukocytes stimulation to produce and release inflammatory mediators such as histamine, LTB<sub>4</sub>, TNF- $\alpha$ , IL-1 $\beta$  and prostaglandin E<sub>2</sub> (Leite et al., 2003). For instance, early work with purified LPS injected at sublethal concentrations in sheep either intravenously or intraarterially resulted in pulmonary arterial pressure to increase and cardiac output to decrease and also caused decreased pulmonary, venous and systemic blood pressure (Mohamed and Abdelsalam, 2008). Further studies in calves have also demonstrated a variety of related physiological effects of the purified LPS to those produced by chemical mediators including prostaglandins, serotonin, thromboxane A<sub>2</sub>, cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) (Emau et al., 1987; Rice et al., 2007; Mohamed and Abdelsalam, 2008). All of these above-listed mediators were considered to be responsible for clinical symptoms correlated with endotoxic shocks (Mohamed and Abdelsalam, 2008).

LPS not only effects the pulmonary system but it also affects the reproductive system of female animals, as several studies have shown bacterial infections in ruminant animals have a negative impact on the physiology of female reproductive system. Therefore, presence of gram-negative bacteria or their endotoxin (LPS) in the uterus causes endometritis in cattle which has negative consequences on the reproduction (Dohmen et al., 2000; Chanrot et al., 2017; Wan et al., 2019). Besides, LPS also causes endometrial reactions, resulting in acute or chronic inflammation that impairs reproductive function and inhibits hypothalamic production of gonadotropin-releasing hormone (GnRH), secretion of luteinising hormone (LH) in the pituitary, and the sensitivity of the pituitary to GnRH in small ruminants, and these changes will cause animals to be less likely ovulating (Sheldon et al., 2009). Most of these reactions involve the secretion of cytokines (interleukins 1, 6, 8 and tumour necrosis factor- $\alpha$ ) (Beutler et al., 2003; Chanrot et al., 2017) that stimulates and attracts innate immune system cells like monocytes, macrophages, neutrophils, eosinophils and natural killer cells into the stroma. LPS also causes dysregulation of prostaglandin secretion and activates endometrial cells to produce

PGE rather than PGF (Herath et al., 2009), PGE2 acts as an inflammatory mediator in pathological conditions that activates the inflammatory response by inducing the secretion of proinflammatory cytokines and various chemokines which cause damage to the endometrial tissue (Herath et al., 2009; Sheldon et al., 2014; Deng et al., 2019).

*P. multocida* and its immunogens LPS have been demonstrated to have pathological effects in the female reproductive system and function which is closely related to *M. haemolytica*. A study by Jesse et al. (2014) stated *P. multocida* type B:2 and its LPS to cause significant changes in the pituitary gland, as well as the reproductive organs and the related levels of hormones in orally inoculated female mice. The pathological findings in the pituitary gland and ovaries were degeneration, necrosis, haemorrhage and oedema. These damages to the cells producing hormones in the pituitary gland and ovaries caused changes in the production of hormones; increased production of progesterone levels and decreased production of oestrogen levels which leads to uncertainty of reproductive status. Therefore, fertility potentials may be low, and animals will not be pregnant due to disruptions in hormone level production. In addition, a study by Ibrahim et al. (2016) revealed the involvement of hemorrhagic septicaemia pathogenesis in the female reproductive system by successfully isolating the bacteria from multiple areas of reproductive system namely ovaries, oviduct, uterine horn, uterine body and vagina as well as the mammary gland and supramammary lymph nodes of infected buffaloes with *P. multocida* type B: 2 subcutaneously. This study suggests *P. multocida* type B: 2 pathogenesis involvement in the female reproductive system in ruminants infected with HS infection.

In another study conducted by Othman et al. (2014) in non-pregnant goats using Gram-positive bacteria *Corynebacterium pseudotuberculosis* revealed that *C. pseudotuberculosis* infection could be implicated in imbalances in the hormonal levels, primarily oestrogen and progesterone, that can lead to infertility. In addition to the hormonal imbalances, cellular changes such as congestion, necrosis, oedema and inflammatory cell infiltration, which in the extent of the infected female goats was varied particularly in the iliac lymph nodes, ovaries and uterus have been observed. *C. pseudotuberculosis* also resulted in elevations of oestrogen and progesterone levels in the goats' blood plasma (Jesse et al., 2015).

Similarly, Khuder et al. (2012) carried on a study to determine the reproductive pathophysiology response related to *C. pseudotuberculosis* and its exotoxin (PLD) in a mouse model. Cellular changes of severe haemorrhage, formation of thrombus, degeneration, vacuolisation and

necrosis has reported this study as well as hormonal imbalances. The ovaries and the uterus showed congestion with infiltration of macrophages and neutrophils, oedema, necrosis and degeneration in the animals inoculated with the life bacteria. In contrast, ovaries and uterus of exotoxin (PLD) inoculated animals had severe congestion, profound thrombus formation and necrosis. The results of this study, therefore, revealed significant variations in sex hormones and changes in the cells of the reproductive organs related to *C. pseudotuberculosis* and its exotoxin phospholipase D (PLD) infection.

These studies suggested that bacterial infections predispose to infertility in affected small ruminant animals. Therefore, pattern recognition receptors are activated by the bacteria and their immunogens that respond to pathogens associated with molecular patterns. These receptors contain toll-like receptors (TLR) and others, and their activation terminates in upregulation of proinflammatory cytokines like IL-1 $\beta$ , IL-18, and tumour necrosis factor- $\alpha$ . These may have direct effects on the uterus and conceptus (Gilbert, 2019).

No studies were performed to investigate *M. haemolytica* effects on the female reproductive system and performance during mannheimiosis in female farm animals. Therefore, further research is needed in this area to investigate reproductive disorders in small ruminants due to *M. haemolytica* and its LPS endotoxin infection.

#### OUTER MEMBRANE PROTEIN (OMP)

The pathogenic Gram-negative bacterial outer membrane is at the interface in both the pathogen and the host that contains more than 100 proteins those have essential roles to play in pathogenesis, and the exact roles of different OMPs in pneumonic pasteurellosis pathogenesis remains to be understood (Davies, 2016). *M. haemolytica* lipoproteins and outer membrane proteins may be associated with serum sensitivity, as they are considered to be significant antigens for protection (Highlander, 2001; Adamu, 2007). *M. haemolytica* has several outer membrane proteins (OMP) which are recognised as surface immunogens that are essential for bacterial adherence and colonisation of the respiratory tract (Pandher et al., 1999). *M. haemolytica*, however, contains an essential outer membrane protein A (OmpA) (Mahasreshti et al., 1997; Kisiela and Czuprynski, 2009). This protein in *M. haemolytica* is also recognised as the heat modifiable outer membrane protein (OMP) or PomA (Mahasreshti et al., 1997; Zeng et al., 1999).

OmpA is involved in cell receptors binding and facilitates many of the pathogenic bacteria to attach to host cells (Kisiela and Czuprynski, 2009). It was suggested based on homology of the sequence that *M. haemolytica* OmpA could play a crucial role in the colonisation of respiratory

tracts of cattle and sheep (Davies and Lee, 2004; Kisiela and Czuprynski, 2009). Further investigation has revealed variations in alleles among OmpA isolated from bovine and ovine *M. haemolytica* strains stating that the OmpA role specificity in these species (Davies and Lee, 2004). The OmpA gene with regard to the variations in the alleles are categorised into four different allelic classes I to IV. Alleles of class I (OmpA1) are almost entirely associated with isolates from bovine *M. haemolytica*, nevertheless classes II to IV (OmpA2 to OmpA4) alleles of *M. haemolytica* only occur in isolates from ovine strains (Davies and Lee, 2004; Hounsome et al., 2011).

*M. haemolytica* also produces a variety of proteins that are iron-regulated outer membrane proteins, including Tbp 1 and Tbp 2 which are pathologically and physiologically important in terms of the acquisition of iron (Ogunnariwo et al., 1997). Since siderophores are not produced in *M. haemolytica*, the primary mechanism for acquisition of iron is the expression of these iron-regulated outer membrane proteins (Ogunnariwo et al., 1997; Kirby et al., 1998; Singh et al., 2011).

*M. haemolytica* and its immunogen OMP involvement in the reproductive performance has to be fully explored, as there is scarce of literatures stating *M. haemolytica* involvement in the reproductive system. However, the closely related bacteria *P. multocida* and its endotoxin LPS involvement in terms of the function and performance of the reproductive system has been discussed in this review. A study by Ibrahim et al. (2018) for assessing clinically and histopathologically, the lesions in the reproductive system in buffalo heifers due to *P. multocida* type B2 immunogens has stated following OMP inoculation; there was congestion and haemorrhage which was significantly higher in the ovaries, cervix, vagina, mammary and supra-mammary glands of buffaloes inoculated subcutaneously, in addition to a significant increase in necrosis severity and degeneration in the ovaries, uterine horn, uterine body, mammary and supramammary glands of the buffaloes. Another study by Jesse et al. (2017b) reported severe histopathological changes in the anterior pituitary gland following challenge with *P. multocida* type B2 subcutaneously and its OMPs both in oral and subcutaneous routes, as well as decrease in GnRH, LH, FSH, estrogen and progesterone hormone concentrations. This study reported the correlation between the lesions of the adenohypophysis, decreased production of hypothalamic GnRH and decreased levels of the hormones LH, FSH, estrogen and progesterone in buffalo heifers inoculated experimentally with *P. multocida* type B:2 and its LPS endotoxin and OMPs. On the basis of these results, *P. multocida* and its immunogens can lead to infertility in buffalo heifers.

There is a gap in research related to the effects of *M.*

*haemolytica* and its immunogens on the reproductive performance and physiology, as vast of studies concentrated on effects in the respiratory system. From this literature review, we have seen some studies conducted on *P. multocida* and its immunogens OMP and LPS has its involvements in the reproductive system physiology and performance. As it is known, Pasteurella and Mannheimia species are closely related together, as both causing pneumonic pasteurellosis in ruminants. By that perspective, we can conclude *M. haemolytica* and its immunogens may have a negative impact on the reproductive performance in both female and male animals. To support, Van der Burgt et al. (2007) reported infertility and endometritis outbreaks in a small dairy herd in the UK which may *Histophilus somni* (previously *Haemophilus somnus*) have involved. The cases were not responsive to treatment with some cows having granular vaginitis and the conception rate in the herd was poor. Therefore, they have concluded that *H. somni* directed to issues of infertility such as granular vaginitis, endometritis and low rates of pregnancy (Van der Burgt et al., 2007). *P. multocida*, *M. haemolytica* and *H. somni* belonging to the family Pasteurellaceae are part of the upper respiratory tract commensals (Gaeta et al., 2017). They are involved in long term effects with negative impacts on production, reproductive performance and fertility (Cernicchiaro et al., 2013; Gaeta et al., 2017).

Therefore, in this field, more research is needed to clarify one of the reproductive disorders in small ruminants that may be caused by *M. haemolytica* and its immunogens and to understand its pathogenesis in the reproductive system of the female animals.

#### PATHOLOGY OF *MANNHEIMIA HAEMOLYTICA* CLINICAL SIGNS

Pneumonic pasteurellosis is a wide range of disease covering around all continents. This disease has an acute febrile course of occurrence with extreme fibrinous or fibrinopurulent bronchopneumonia, fibrinous pleurisy, and septicaemia (Abdullah et al., 2015). Young animals are susceptible to the disease more than the adults, and they develop more serious infection where sudden death can happen with or without any prior clinical signs (Chung et al., 2015). Clinically, cattle with *M. haemolytica* respiratory infections may experience or suffer from fever, cough, nasal discharge and respiratory distress combined with inappetence and loss of weight (Rice et al., 2007). In the early stages of the disease, the respiratory rate rises accompanied by dyspnoea that in some cases, causes oral breathing and expiratory grunting (Yates, 1982). Moreover, animals with the disease soon develop high fever (40-41°C), anorexia and rapid shallow respiration accompanied by mucopurulent nasal discharge and subsequently productive cough that normally occurs in most affected animals emphasised by movement or physical effort (Kabeta et

al., 2015). In severe cases, however, infected animals will die as a consequence of toxæmia that occurs even before major pulmonary lesions development. Sudden death, in this case, is considered to have been the first indication of acute outbreaks in this situation, primarily young calves (Mohamed and Abdelsalam, 2008).

An acute outbreak of pneumonic pasteurellosis in sheep and goats flock normally begins with one or more death cases, specifically when lambs and kids are at risk, and sheep and goats were having obvious respiratory disease symptoms. These latter suffer tremendously from high temperatures (> 40°C) and dyspnoea, and observing the rest of the flock will demonstrate a mild respiratory disease such as coughing and oculo-nasal discharges. Animals recovering from the disease, development of chronic lung lesions may be observed, and they may remain unthrifty afterwards (Gilmour, 1980). The possible effects on the reproductive system after infection with *M. haemolytica* in animals are to be discovered, as studies mainly concentrated on the effects of the pulmonary. We hypothesise that after recovery from pneumonia due to Mannheimia will affect negatively on the reproductive performance of the animal.

Pneumonic pasteurellosis can affect severely in lambs and kids, clinical signs of fever, lethargy, dyspnoea, reduced appetite can be observed, and sudden death is more common in young animals. Those animals who survive from the acute phase of the disease may recover, or they may become chronically infected with the disease have reduced lung capacity and impaired weight gain, and the occurrence of sporadic deaths tend to be a serious issue (Chung et al., 2015).

#### POST MORTEM CHANGES AND HISTOPATHOLOGICAL LESIONS

Among infected small ruminants with pneumonic pasteurellosis, the most noticeable gross lesions that can be found are the marbling of the lung, presence of excess straw-coloured fluid in the thoracic cavity, as well as the appearance of frothy exudates in the trachea, bronchi and damaged lungs surface (Jesse et al., 2019). Pulmonary lesions are always bilateral with the distribution of cranioventral, while the most affected portions are below the horizontal line generally by the trachea bifurcation, apical and the cardiac lobes. Infections affecting large parts of the diaphragmatic lobe may be more common in severe cases (Mohamed and Abdelsalam, 2008). Furthermore, fibrin and oedema fluid accumulation areas in interlobular septa and alveoli are the most evident lesions. The lesions consisted of congestion, consolidation, hardness, raised red to bronze areas up to 1 cm in diameter and fibrinous pleuritis (Ames et al., 1985; Chung et al., 2017). Acute fibrinous haemorrhagic pneumonia with pleurisy adhesions, however, are the basic post mortem lesions (Daoust, 1989). Besides, numerous areas of coagulative necrosis are

commonly found within the portions of the pneumonic lung parenchyma appearing in irregular shape and clearly demarcated with white borders that are thick and have deep red central zone (Mohamed and Abdelsalam, 2008).

In calves, the pulmonary lesions in the affected lobules of typical bovine pneumonic pasteurellosis are reddish-black, hard and elevated above the normal surface of the lung. There is generally distended septa and a dull fibrinous exudate on the visceral pleura, and there are two to three litres of straw-coloured thoracic fluid in some affected lungs, and there is emphysema with bullae formation (Stockdale et al., 1979).

In adult cattle, Pathological changes due to mannheimiosis have been studied extensively. *M. haemolytica* causes fibrinous bronchopneumonia characterised by exudate mainly consisting of fibrin inside the lumen of bronchi, bronchioles and alveoli with coagulative necrosis and interlobular-septal oedema (Zhang et al., 2020). Lung lesions consisting of purple-red or grey consolidation with small haemorrhagic foci in the ventrocranial and accessory lobes with gelatinous interlobular septal expansion has been reported (Yaman et al., 2018). Fibrinous pleuritis and coagulative necrosis areas can be seen as well as pleural thickening and adherence of the lungs to the chest wall with Mucopurulent exudate in the small bronchi and bronchioles (Yaman et al., 2018; Blakebrough-Hall et al., 2020). Histopathological findings consisting of proliferative changes in the lung parenchyma characterised by type-II epithelial cell proliferation in the alveoli with dense infiltration in the alveoli and bronchioles, neutrophils and mononuclear cells mixed with fibrin has been reported, in addition to the observation of fibrin plugs in the lymphatic vessels and venules (Yaman et al., 2018). Furthermore, congestion, haemorrhage, oedema, and atelectasis with alveolar spaces filled by cellular infiltrate and proliferation of type II pneumocytes (Yaman et al., 2018; Ola et al., 2020)

The presence of *P. multocida* and its immunogens in other structures of the body apart from the respiratory system has been confirmed (Annas et al., 2014, 2015). Marza et al. (2017) stated that *P. multocida* B2 LPS is capable of crossing the blood-brain barrier and inducing pathological lesions in multiple areas of the nervous system of the buffalo calves challenged with LPS. The authors have reported mild congestion in the cerebrum in this study as well as in the brainstem, the rest of the nervous system was observed to be normal in these animals inoculated with 10 ml of LPS broth extract from *P. multocida* B2 orally. In contrast, animals challenged with 10 ml of LPS broth extract from *P. multocida* B2 intravenously has revealed encephalitis with severe brain congestion, especially in the cerebrum and brainstem, whilst the cerebellum was less

affected, and there was slight congestion in the meninges.

Also, Ibrahim et al. (2018) has stated histopathological alterations in the reproductive organs of buffalo calves, including oedema, congestion and haemorrhage, necrosis and degeneration and inflammatory cell infiltration. Histopathological changes were observed primarily in the ovary, uterine body, uterine horn, oviduct and supramammary lymph node, while there is affection in the cervix, vagina and mammary glands.

We can conclude that there is an association between *P. multocida* and the performance of the reproductive system in female animals with reference to the literature stated above. Similarly, *M. haemolytica*, which is closely associated with *P. multocida*, its involvement in the reproductive system of female animals has to be discovered, and the possible effects on the reproduction.

## CONCLUSION

*M. haemolytica* is normal commensal on the respiratory tract of animals, with the interaction of many variables, including mostly environmental stress with viral or bacterial agents, trigger the bacteria from its commensal state into a pathogen causing pneumonic pasteurellosis. Previous studies were concentrated on *M. haemolytica* involvement in the respiratory system, and its effects on the respiratory tract, but its involvement in the reproductive system is not studied well, and there is lack of information related the bacterial involvement and its immunogens (LPS and OMP) on the reproductive system. As the above-mentioned studies highly suggest that Gram negative bacteria and their immunogens may have adverse effects on infected animals, which may impair their reproductive functions as well. Therefore, future studies have to be conducted on the *M. haemolytica* bacterium and its immunogens effect on the various parts of the reproductive system and its physiological changes.

## AUTHORS CONTRIBUTION

All authors contributed equally and approved the final manuscript.

## CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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