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Pasteurella multocida and *Mannheimia haemolytica*; virulence factors, diseases, and notably increasing antibiotic resistance rate among their isolates: a comprehensive review

Adam Bashir Tawor[1,2], Osman Erganiş[1], Canan Kebabçioğlu[1], Suliman Mohamed Yousof Sadam[3]

1.Department of Microbiology, Faculty of Veterinary Medicine, University of Selçuk, Konya, Türkiye. **2.** Department of Microbiology, Faculty of Veterinary Science, University of Al Gadarif, Al-Gadarif, Sudan. **3.** Department of Animal Production, Faculty of Veterinary Science, University of Al Gadarif, Al-Gadarif, Sudan.

Tawor, B. A. ORCID ID: 0000-0001-6865-1801; Erganiş, O. ORCID ID: 0000-0002-9340-9360; Kebabçioğlu, C. ORCID ID: 0000-0001-7299-9923 ; Sadam S. M. Y. ORCID ID: 0000-0001-5806-7281

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ABSTRACT

The current review on *Pasteurella multocida* and *Mannheimia haemolytica* tried to shed light on these two organisms due to their medical and economic importance as well as to their elevating antibiotic resistance rate among the isolates from animals basically cattle, sheep, and goats. In this comprehensive review, we screened both old and recently published works that are available electronically on authorized scientific sites. Here we provide the latest data on those organisms their structure, suitable growth conditions, virulence factors, pathogenesis, their associated diseases, and their distribution along with antibiotic resistance emergence and the possibility of more new emergences of resistant isolates among species of both organisms. Lastly, we reviewed all the old and modern methods for diagnosis, controlling, and preventing the occurrence of diseases caused by these organisms besides studying and reviewing the effective ways to manage antibiotic resistance issues. Our review concluded that more specific research is needed to shed light on phenotype and genotype differences among those organisms, some issues should be subjected to intensive investigations and research focus such as emerging and re-emerging infectious diseases caused by these organisms and antigenic variants between agents. Evaluation of innate and adaptive immunity after infections or vaccinations is important for producing more specific drugs or vaccines in the future.

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Introduction

1. *Pasteurella multocida* (*P. multocida*) and *Mannheimia haemolytica* (*M. haemolytica*) are worldwide spread Gram-negative coccobacilli bacteria that exist in the same family (Pasteurellaceae) that are responsible for many diseases in animal species more intensively in cattle and sheep leading to a huge loss in the livestock sector (Abd-Elsadek et al., 2021). According to WOAH (World Organization for Animal Health), about 20% of bovine deaths come from Pasteurella infections WOAH (2020). Both microrganisms are found on the surface of the respiratory tract as commensal microflora but can

*Corresponding Author: Adam Bashir Tawor
E-mail: 193146002003@lisansustu.selcuk.edu.tr

proliferate and act as an opportunistic pathogen in case of association with other illnesses or any condition that could predispose infection by dropping the immune system defense mechanisms (Abbas et al., 2023; Hsuan et al., 1999).

Different strains of *P. multocida* are multi-species organisms which causes very serious illness in animals like hemorrhagic septicemia (HS) in cattle and buffalo, fowl cholera, atrophic rhinitis in swine, snuffles in rabbits, enzootic calf pneumonia and shipping fever (bovine respiratory disease). Although some of these diseases are classified as multifactorial diseases (Mahrous et al., 2022); till now no epidemiological study clearly explained the role of *P. multocida*. Pasteurellosis is one of the zoonotic diseases; Human cases of Pasteurellosis usually are due to bites or scratches by pets-animals or by getting contact with contaminated animal food or other belongings (Hanafy et al., 2022; Omaleki et al., 2016). *M. haemolytica* formerly had been classified as *Pasteurella haemolytica* type A until Angen and his colleagues had reclassified it in a separate genus (Angen et al., 1999a). Bovine respiratory disease (also known as shipping fever) is a major disease that comes as a result of infection with *M. haemolytica* and other etiologies in addition to septicemia and pneumonia in sheep and goats, also sheep mastitis has been reported to be caused by *M. haemolytica*. Some studies suggest that *M. haemolytica* can form biofilm on epithelial cells of the respiratory system (Amat, 2019).

2. Historical background

The organism had been identified for the first time by French chemist Louis Pasteur in 1880 when he had worked on fowl cholera, so named after his name as Patsteurella (Pasteur, 1880). According to recent classification *P. multocida* has been grouped into three subtypes they are; *P. multocida* subsp. *multocida*, *P. multocida* subsp. *gallicida*, and *P. multocida* subsp. *Septica*. *P. multocida* divided to five different serotypes (A, B, D, E, and F) based on capsular polysaccharides such as hyaluronic acid, heparin, arabinose, mannose, galactose and chondroitin. These serotypes again divided according to their lipopolysaccharides to 16 different serovars from (1 to 16) (Harper et al., 2006). *M. haemolytica* previously had been isolated for the first time from bovine pneumonia in the 1920s and classified as *Pasteurella haemolytica* to be distinguished from none haemolytic one (Jones, 1921).. *P. haemolytica* had two distinct biotypes: A biotype, which ferments arabinose, and T biotype, which ferments trehalose. The T biotype was later reclassified as *P. trehalosi* and eventually placed into a separate genus called *Bibersteinia trehalosi* (Blackall et al., 2007).

Angen and his colleagues re-identified *P. haemolytica* to be *M. haemolytica* (Serotypes 1, 2, 5–9, 12–14, 16, and 17). *M. haemolytica* serotypes seem to be closely related to each other, especially S1, S2, and S6 on serologic and genetic bases, but sing molecular techniques for specific genes has revealed the differences between these strains (Angen et al., 1999b; Davies & Lee, 2004).

3. Bacteriology and growth conditions

P. multocida and *M. haemolytica* are Gram-negative, non-motile, non-spore-forming small facultative coccobacillus both of them are members of the family Pasteurellaceae. Organisms grow well at 37°C on blood agar and also can be grown on dextrose-starch, casein-sucrose-yeast (CSY), chocolate, Mueller-Hinton, or brain heart infusion (BHI) agar, however, there is no growth on MacConkey agar. *M. haemolytica* is producing β-hemolysis on blood agar (Garzon et al., 2023; Rice et al., 2007).

Most clinical isolates of *P. multocida* are catalase, oxidase, indole, and ornithine decarboxylase positive. Also, isolates can ferment sucrose and glucose without gas production and reduce nitrate to nitrite on biochemical bases. *M. haemolytica* fail to ferment D-mannose which is first step to differentiate it from *P. multocida* (Carter & Cole Jr, 2012).

4. Virulence factors

Tremendous virulence factors are possessed by *P. multocida* and *M. haemolytica*. As shown in Table 1

Table 1. Some important immunogenic factors of both *P. multocida* and *M. haemolytica*

Factor	Origin	Mechanism	Immunogenicity action
Capsule	Bacterial surface	Antiphagocytic and resistance of lysis	Weak
Leukotoxin	Secreted	Leukocyte necrosis	Strong
LPS	Bacterial cell wall	Proinflammatory	Lipid A is strong
OmpP2	Outer membrane	Biofilm formation and adhesion	Weak
OmpA	Outer membrane	Adherence to lactoferrin	Strong
PlpE	Outer membrane	Unknown	Strong
Biofilm (*M. haemolytica*)	Surface proteins (adhesins)	Antibiotic resistance and escape immune response	Generally weak

these factors are similar to each other due to their mutual origin, however, some genetic differences between those factors like molecular weight, protein synthesis pathways, and mode of action have been disclosed (De la Mora et al., 2007).

4. 1. *P. multocida*

4.1.1. Capsule

P. multocida has five different capsular groups according to the capsular polysaccharide they possess. The genes encoding for these strains was assumed to be located in a single region on the genome until studies done by DeAngelis and White showed that capsules of strain A and B were encoded from different region, so they concluded that may refer to farther capsule variation in future (DeAngelis & White, 2004; Mirtneh et al., 2022). The main role of the capsule is the resistance to phagocytosis and resistance to complement-mediated lysis (innate immunity) mainly through expressing hydrophilic substrate (Boyce et al., 2000; Guan et al., 2020).

4.1.2. *Pasteurella multocida* toxin (PMT)

This toxin is about 146 - kDa protein encoded on lysogenic bacteriophage existing only in the genome of the toxin-producing strains (type D strain; the causative agent of atrophic rhinitis in swine). The toxin is released upon bacterial lysis and inters host cells via receptor-mediated endocytosis (Pullinger et al., 2004). The role of PMT in pathogenesis is the activation of some proteins in the cytoplasm of host cells such as G proteins, (Gq and G12/13) and Cβ. These interactions between protein pathways result in activation of specific signal transduction pathways which lead to cytoskeletal changes, inhibition of osteoblast maturation and activation of the mitogen activating protein. PMT may also obstacle the migration of dendritic cells to lymph nodes (Kitadokoro et al., 2007).

4.1.3. Iron acquisition proteins

Iron is a very important compound for survival of bacteria; *P. multocida* has many different ways to acquire iron from host depots such as ferric hydroxides, hem, and transferrin. Acquiring iron requires a specific outer membrane receptor and a periplasmic-binding protein. Siderophores are the keyword in the iron acquisition process; these compounds are normally possessed by many microorganisms. It can be classified into three structural types: hydroxy carboxylate, catecholate, or hydroxamate. Only one siderophore, named multocidin, is unique to *P. multocida* (Boyce et al., 2010). Recent study has shown that lacking of some iron acquisition protein genes such as HgbA and HgbB genes may lead to forming of nontypical *P. multocida*, eventually, *P. multocida* may change or lose its capsule due to shortness or absence of iron acquisition proteins (Balevi et al., 2023).

4.1.4. Lipopolysaccharide (LPS)

LPS generally is a very important component of Gram-negative bacteria rich with variability in polymeric O-antigen repeats, but with exception of *P. multocida*; there is a lack of O-antigen repeats. LPS of *P. multocida* is varied from one strain to another for example LPS of strain A differs from other strains LPS. Also, LPS fails to induce the same immune response in two different animal species and therefore no heterogenous immunity can be induced (Harper et al., 2011; Mombeni et al., 2021).

4.1.5. Fimbriae and adhesin

Full genome sequencing of P. multocia pm70 had been carried out, it revealed that all types possess in their genome many genes such as (ptfA, flp1, and flp2) that encode for different types of fimbriae (May et al., 2001). Although *P. multocida* genetically has different genes and different types of fimbriae, they functionally do the same role in pathogenesis by attaching to surfaces of the respiratory tract and adhering to host cells (colonization and invasion) (Yanthi et al., 2021).

4.1.6. Sialic Acid metabolism

Sialic acid has several roles in the pathogenesis of *P. multocida* including stabilization of membranes and regulation of transmembrane receptors function. Bacteria can utilize host sialic acid as a carbon and nitrogen source by sialidases enzyme. Existing of sialic acid may enhance the ability of bacteria to avoid the immune system of the host by blocking some receptors or altering some molecules features (Vimr et al., 2004).

4.1.7. Hyaluronidase

Hyaluronidase enzyme assumed to play important role in pathogenesis of *P. multocida* usually produced by type B strain that causing hemorrhagic septicemia in buffaloes and cattle. HA is thought to function as a "spreading factor" by degrading hyaluronic acid on host cells, thus allowing the spread of bacteria in tissues (Carter & Chengappa, 1980). Type A and B strain especially B: 2 strain is the only type that produces this enzyme so some researchers suggest it may be a useful tool for diagnosing and differentiating type B: 2 strain of *P. multocida* (Chung et al., 2001; Raj et al., 2023).

4.1.8. Outer membrane proteins (OMPs)

OMPs of *P. multocida* was identified firstly as one of five important immunogens able to evoke an immune response, it is mass about 37kDa; monoclonal antibody produced against this protein enhanced immunity of rabbit and protected from homologous

challenge; but for heterologous strains, some limitations have been noted. The main role of these outer membrane proteins is facilitating adherence of invading organisms to host cell surfaces. The major outer membrane proteins of *P. multocida* are OmpH, OmpA, Oma87, Pm1069, iron related proteins, and Tbp (transferrin binding protein) (Gogoi et al., 2018), recently (Zhao et al., 2021) approved that pcgD outer membrane has a critical role in P. multocida infection.

Biofilm formation has been reported for the first time by (Petruzzi et al., 2017). They confirmed the ability of *P. multocida* serogroup A to produce a type of biofilm in vitro, produced biofilm is smooth and thicker than biofilm produced by other encapsulated bacteria. In the same trial, they suggested that capsular polysaccharide (CPS) may interfere with biofilm formation by blocking the adherence of bacteria to the surfaces or by preventing the EPS matrix from encasing large numbers of bacterial. In a different study (Petruzzi et al., 2018) experimentally found that *P. multocida* was able to produce biofilm in vivo on avian pulmonary tissues and suggested that it may be correlate to chronic infections of fowl cholera.

4.2. *Mannheimia haemolytica* and LPS

M. haemolytica produces many types of capsular antigens it differs according to serotype of the organism for example S1, S9, and S12 but generally they evoke host immune responses besides it is main role in avoiding phagocytosis by macrophages. LPS extremely necessary for *M. haemolytica* pathogenesis it has a classical endotoxic activity able to stimulate pro-inflammatory mediator production and inflammation specially O-antigen which is known to be the most immunogenic component of LPS (Table 1). activation of these inflammatory substances results in damaging endothelium layers and causing vascular leakage (Confer & Ayalew, 2013; Kamarulrizal et al., 2022).

4.2.1. Outer membrane proteins (OMPs)

This compound structure of OMPs maintains the hemostasis of bacterium by controlling the influx and efflux of nutrients in addition to coordinating signals transduction. There are different types of outer membrane proteins with different functions, basically they act as adhesin factors or iron acquisition proteins, the function of some proteins is still unknown. Examples of these proteins are PlpE, PlpF, OmpA, and OmpP2 (Avalos-Gómez et al., 2020).

Members of the OmpA family of proteins resemble a good model for vaccine production for several bacteria. *M. haemolytica* OmpA is an approximately 30 kDa, heat-modifiable, it was found to be a highly immunogenic protein with porin activity. Members of the OmpA protein family share some features such as homology with heat-modifiable OMPs protein from numerous bacteria (Confer & Ayalew, 2013; Ujvari et al., 2019). OmpA protein has adhesin properties and recently had been identified as a binding factor to lactoferrin (Zhang et al., 2016). Although a lot of these proteins are not immunogenic, they potentially trigger immune response for producing opsonizing antibodies which afforded protective against *M. haemolytica*. Transferrin binding proteins B family also remove iron from transferrin, mostly outer membrane immunogens are strong immunogens (Samaniego-Barrón et al., 2016).

4.2.2. Adhesins

M. haemolytica adhesins include a 68 kDa glycoprotein, N-acetyl-D-glucosamine (MhA) that responsible for adherence to epithelial cells of trachea and activates the oxidative burst of host neutrophils through glycoprotein receptor, it has major role in colonization of respiratory tract surfaces. *M. haemolytica* produces this adhesin more intensively when cultivated at 41°C (Wynn & Clawson, 2022; Zhang et al., 2016) in addition to this many types of antigens act as adhesins such as OmpA, lipoprotein1, Filamentous hemagglutinin and fimbriae (Kisiela & Czuprynski, 2009).

4.2.3. Toxins

M. haemolytica is known to produce leukotoxin (LKT) since it associated with infection in bovine respiratory disease where serious damage on host macrophages and neutrophils has been reported (Maheswaran et al., 1992). Four genes are coding for leukotoxin (lktC, lktA, lktB, and lktD) lktA codes for the structural toxin, and lktC codes for activation, whereas products of lktB and lktD are coding for secretion of toxin (Rice et al., 2007). LKT is the most important virulence factor in *M. haemolytica* – induced pneumonia. LKT is also responsible for hemolysis in vitro, toxin is produced by all serotypes of the bacterium except the mutant one (LKT – deficient mutant) (Confer & Ayalew, 2018).

4.2.4. Biofilm formation

Biofilm concept refers to a type of microorganism arrangement, often in two different levels the first one is attachment of microorganisms to each other and secondly attaching to adjuvant surfaces here adherent bacteria become embedded within a slimy extracellular matrix mainly in shape of extracellular polymeric substances (EPSs) (Montes García et al., 2018; Olson et al., 2002). These biofilms protect the bacterial cells against the host immune response and antibiotic treatment bacteria within a biofilm are more resistant to antibiotics than planktonic cells.

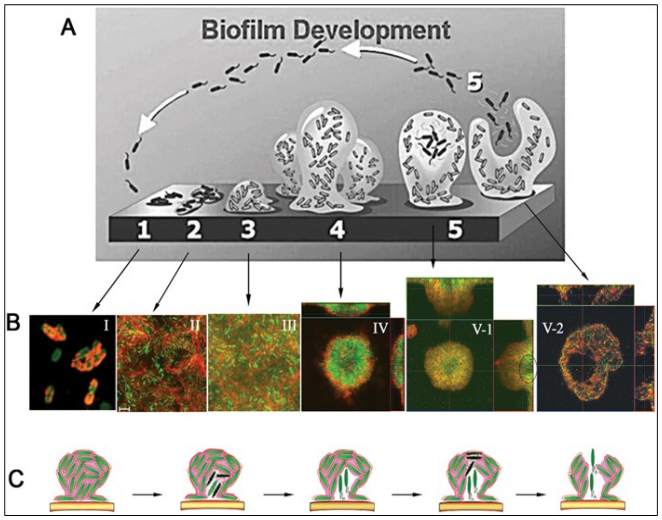

Figure 1. Stages of biofilm development.
Initial attachment, (2) Irreversible attachment, (3) Maturation I, (4) Maturation II, and (5) Dispersion. Each stage of development in the diagram is paired with a photomicrograph of a developing P. aeruginosa biofilm created by P. Dirckx, K. Sauer, and D. Davies (100).

Production of biofilm in *M. haemolytica* has been reported in bovine respiratory disease (Boukahil & Czuprynski, 2016; Kandimalla et al., 2022).

4.2.5. Produced enzymes

M. haemolytica secreted numerous enzymes that participated somehow in pathogenesis. Neuraminidase (sialidase) is a major extracellular protein associated with many bacterial species; it acts on sialic acid residues of host mucosal sialo-glycoprotein exposing underlying carbohydrate moieties used for bacterial adhesion. Neuraminidase has a role in enhancing bacterial adherence to cell surfaces that have been affected by this enzyme action.

M. haemolytica genes also code for O-sialoglycoprotease enzyme which hydrolyzes peptide bonds within glycoproteins. Studies found that homologs of the protein were detected in several Gram-negative bacteria; however, secretion in the form of O-sialoglycoprotease was restricted to *M. haemolytica* serotypes (Klima et al., 2018). Protease recently has been detected on supernatant from *M. haemolytica* culture it is responsible for cleaving of host immunoglobulins, especially IgG1into 39,12 and 7 kDa bands whereas no effect on IgG2 has been recorded (Kotelnikova et al., 2016a).

5. Pathogenesis

5.1. *P. multocida* pathogenesis

Although *P. multocida* possesses a huge set of virulence factors the mechanism of action for some of them is still anonymous. Induced diseases and susceptible hosts are so variable with strong specificity it may be due to strain, adaptation, possession and expression of specific virulence factors. Also host factors such as anatomic features and innate immunity, above all the ecology factors which partially neglected in studies on *P. multocida* infections (Harper et al., 2006; Peng et al., 2019).

P. multocida is an opportunistic pathogen that normally colonizes surfaces of the respiratory tract of hosts so it directly moves down into tissues after association with suitable predisposing factors. Studies on fowl cholera suggest that mucosal membranes may act as a portal of entry, the same for open wounds (Pattison et al., 2007).

Firstly *P. multocida* attaches to host cells using adhesins, which are surface proteins that bind to specific receptors on the host cell surface. Secondly one of the crucial steps in the pathogenesis of systemic disease is resistance of phagocytosis by bacterial capsule; the capsule has two major roles in pathogenesis; one is producing hyaluronidase enzyme that degrades the hyaluronic acid of the host cell to facilitate entering into tissues leading to necrosis and cellulitis, and the other one is avoiding lysis through complement system proteins. Also one of important steps in *P. multocida* pathogenesis it is ability to invoked a high inflammatory response when growing in any parenchymatous tissue this damage usually is local as abscesses (Diallo & Frost, 2000; Smallman et al., 2024); found evidence for multiplication of *P. multocida* on blood in vivo. However, some strains survive in vitro in serum with active complement proteins and they think growing in serum did not necessary correlate with virulence in avian strain of *P. multocida*. In fowl cholera and hemorrhagic septicemia usually, animals death is attributed to spreading petechiae on serosal and epicardial surfaces, which indicates consumptive coagulopathy common to many endotoxemias.

P. multocida produces various toxins, dermonecrotic toxin (in atrophic rhinitis in pigs), leukotoxin, these toxins can damage host cells, disrupt the immune response, and promote bacterial survival and dissemination, beside that also *P. multocida* can modulating cytokine production that result in can manipulate the immune response to its advantage (Boyce et al., 2010; Sahoo et al., 2020).

5.2. *M. haemolytica* pathogenesis

M. haemolytica has a variety of virulence factors involved in pathogenesis process as a general mechanism of these factors resemble its counterparts in other Gram-negative bacteria, few differences may exist depending upon bacteria-host interaction mechanisms. Infection with *M. haemolytica* is

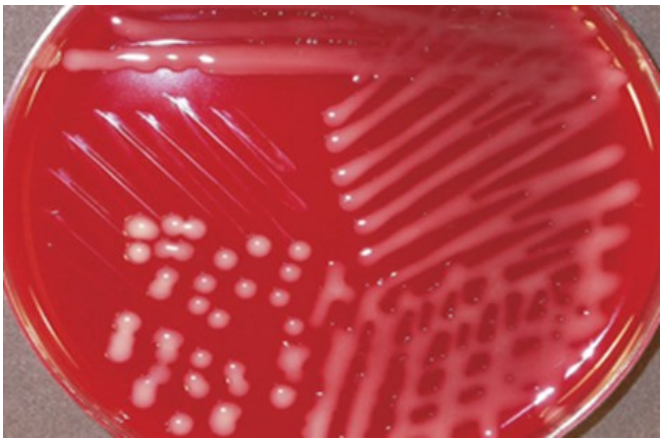

Figure 2. P. multocida on blood agar. Photo taken from atlas.sund.ku.dk

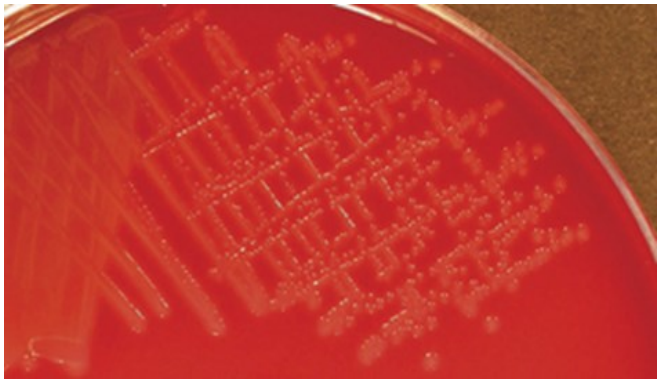

Figure 3. *M. haemolytica* on blood agar. (101)

reported to be related specifically with ruminants (Confer & Ayalew, 2018). Classic immunogens such as capsule, LPS, toxins and neuraminidase are major factors contributing in clinical manifestation of *M. haemolytica* infections (Rice et al., 2007).

Routes of entering same as for *P. multocida* through respiratory tract after association with viral diseases and/or other illness that pave the road for their proliferation and invasion of tissues. Unlike *P. multocida*, *M. haemolytica* has limitations in infected hosts and produced clinical cases (Gelasakis et al., 2015). Capsule and surface proteins are very important in colonization of bacteria. Penetration of epithelial cells is facilitated by secretion of neuraminidase enzyme which is an extracellular protein present in many bacterial species. Its role involves cleaving sialic acid residues from host mucosal sialoglycoproteins, which exposes underlying carbohydrate structures that bacteria use for adhesion. This mechanism is crucial for bacterial attachment to host cells and tissues (Zhao et al., 2023). *M. haemolytica* neuraminidase was demonstrated to be a large, approximately 160 kDa, extracellular, enzyme produced by different serotypes, mainly during stationary growth phase (Highlander, 2001; Klima et al., 2014) Neuraminidase is produced in vivo in *M. haemolytica*-infected cattle as evidenced by the rise in anti-neuraminidase antibodies during infection (Briggs et al., 2021; Confer & Ayalew, 2018).

Several proteases were recently identified in the culture supernatant of *M. haemolytica* S2, and those were primarily cysteine proteases or metalloproteases (Rico et al., 2017).

Proteases that can break down IgG have been found in Streptococcus pyogenes, *Pseudomonas aeruginosa*, *Proteus mirabilis*, and Staphylococcus *aureus*. Although a search of the genome databases of 10 *M. haemolytica* did not reveal a specific IgG protease, the presence of multiple endopeptidases suggests the potential for IgG cleavage. Furthermore, (Ayalew et al., 2017)) identified a potential IgA

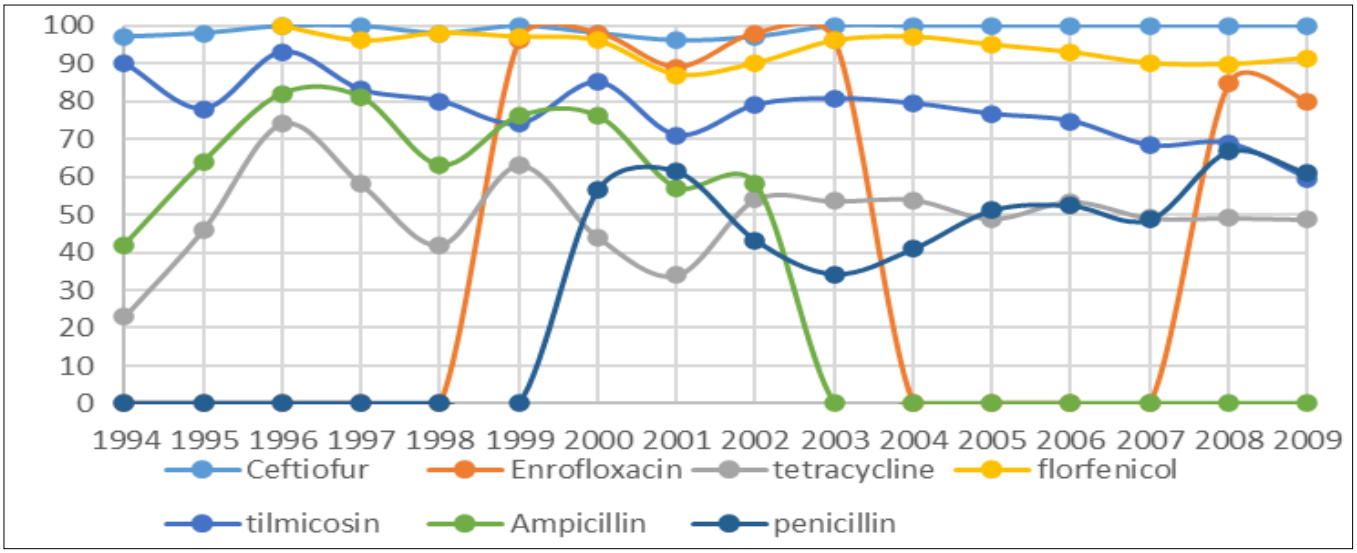

Figure 4. Susceptibility of *Pasteurella multocida* and *Mannheimia haemolytica* to some antibiotics within fifteen years

protease in *M. haemolytica* culture supernatant using proteomic analyses. IgA proteases in other bacteria are typically associated with autotransporter molecules, facilitating bacterial invasion of mucosal surfaces and evasion of host defenses. Bacterial IgA proteases are also known to be immunogenic, triggering the production of local and systemic antibodies in infected hosts (Kotelnikova et al., 2016b). The gene encoding sialoglycoprotease and its enzymatic activity were linked to various serotypes of *M. haemolytica*, with similar proteins found in several Gram-negative bacteria. However, the secretion of O-sialoglycoprotease was specific to *M. haemolytica* serotypes Vaccination of calves with a recombinant sialoglycoprotease-fusion protein induced antibody production against the protein (Shewen et al., 2003). Antibodies against sialoglycoprotease were detected in the sera of cattle challenged with live *M. haemolytica* (Lee et al., 1994; McGill & Sacco, 2020). The exact role of sialoglycoprotease in respiratory pathogenesis remains unclear. Studies have shown that it can cleave cell surface glycoproteins such as CD34 (present on hematopoietic progenitors and endothelium), CD43 (leukosialin found on leukocytes), CD44 (a receptor for hyaluronic acid involved in cell adhesion), CD45 (a leukocyte common antigen involved in signal transduction), and platelet selectin (Ramírez-Rico et al., 2024).

Leukotoxin has been subjected to intensive studies since in vitro damage by *M. haemolytia* toxin had been reported on bovine neutrophils. Leukotoxin type A lyse cells mainly through pores formation; leads to the efflux of K+ and influx of Ca2+ leading to swelling and eventual cell lysis, apoptosis and mitochondrial dysfunction (Atapattu & Czuprynski, 2005; Hsuan et al., 1999). Dominant chemokines in production of pro-inflammatory response are cytokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1β and IL-8. Researchers suggest that LPS has basic role in cytotoxicity of macrophages and monocytes (Jeyaseelan et al., 2000).

Biofilm formation is one *M. haemolytica* tools to persist and invade respiratory system. Conducted in vitro trials was found that OmpA adhesin is the main factor that facilitates attachment of *M. haemolytica* to plastic surfaces so OmpA considers the first step toward biofilm formation (Boukahil & Czuprynski, 2015) and (Kisiela & Czuprynski, 2009) reported in their study that lipoprotein 1 (Lpp1) also has a role in attachment of *M. haemolytica* to bovine epithelial cells. (Boukahil & Czuprynski, 2015); took advantage of this knowledge (adhesins role in biofilm formation) to design blocking substances such as monosaccharides to compete with bacterial adhesins in attaching to host cells surfaces this resulted in inhibition of bacterial adhesins and obstacles biofilm formation.

6. Epidemiology

6.1. *P. multocida*

Theodore Kitt in 1885 first described the causative agent called Bacterium bipolare multocidum, later Bacillus bovisepticus by Flugge in 1896. In 1900 Lignieres proposed the name *Pasteurella*, Pasteurella *haemolytica* was given by Newsom and Cross in 1932 and this has also been well accepted (Rehmtulla & Thomson, 1981). Incidence of *P. multocida* is high globally and so distribution of serotypes and serovars of this organism. Despite intensive studies on this pathogen neither developed countries nor undeveloped counties have ultimate way to remove clinical manifestations of this pathogen. Outbreaks redundantly have been reported in tropical regions more specifically in Asia and Africa as hemorrhagic septicemia and fowl cholera diseases which are caused by *P. multocida* strain B and strain A respectively (Moustafa et al., 2015).

Morbidity and mortality of shipping fever average approximately 14 and 1% respectively (USDA National Animal Health Monitoring System (NAHMS) (Storz et al., 2000) revealed in their study the important role of coronavirus in shipping fever wherein two different outbreaks high percentage of association of respiratory bovine coronavirus with shipping fever had been reported as 61% and 74%. Their study recommended that vaccination and management methods against shipping fever should consider and include this virus as main factors in the infection.

Diseases of *P. multocida* in livestock are varying in clinical features and animal species, most important diseases besides (BRDC) are hemorrhagic septicemia (HS) in cattle and buffaloes, fowl cholera in poultry, atrophic rhinitis in pigs and snuffles in rabbits, pneumonic and septicemic Pasteurellosis. Generally, Pasteurellosis has roughly 100% mortality in endemic areas of Africa and Asia (OIE 2009). Deaths usually occur in older calves and young adults alike. In non-endemic areas, massive epizootics may occur with a high morbidity rate may reach up to 100% if treatment is not applied at an early stage of disease onset (Benkirane & De Alwis, 2002). As for Fowl cholera it is a very serious disease with a mortality rate reach to 90% disease had been recorded in Europe since the 18th century. Outbreaks of fowl cholera associated with high mortality are typically seen in laying flocks (Singh et al., 2014). Several studies carried out on diversity of *P. multocida* associated with fowl cholera outbreaks; the findings of such epidemiological studies

vary in their outcome, and some outbreaks are associated with a single genotype for several years (Singh et al., 2013). However, outbreaks with multiple genotypes have been reported in turkeys this contradiction some reports suggest problems in Heddleston serotyping method (reproducibility or stability). Overall, the evidence of study carried by (Singh et al., 2014). Researchers strongly suggested a single strain of *P. multocida* causing these repeated outbreaks of fowl cholera. They identified *P. multocida* by PCR then serotyped isolates using the Heddleston scheme and genotyped using both multilocus sequence typing (MLST) method and an enterobacterial repetitive intergenic consensus (ERIC)-PCR method. Kumar and his colleagues hypothesized that the variation in the distribution and occurrence of *P. multocida* infections in different agroclimatic regions of India includes different species of animals and avian species. They also observed outbreaks throughout the year regardless of the season. Their findings contradict the notion that HS mostly occurred during the monsoon or post-monsoon period and this is consistent with the previous findings (Kumar et al., 2004; Loneragan, 2001). Globally serotype B is second dominant strain in fields after type A strain of *P. multocida*. Hemorrhagic septicemia causing strain in Africa is prevalently caused by B strain and strain E is most dominant in Asia but some studies showed that both B and E are isolated from Africa and Asia from clinical cases of *P. multocida* infections (Smith et al., 2021).

In Europe, although HS is uncommon diseases which firstly been reported in pigs in Spain; *P. multocida* has been intensively studied from clinical to advance genetic approach levels especially in bovine respiratory complex (Borge et al., 2011). All epidemiological studies assure that *P. multocida* is a ubiquitous organism that lives as commensal on surfaces of respiratory tracts of animals acts as an opportunistic pathogen cannot clinically induce diseases alone unless in presence of predisposing factors such as Mycoplasma species most relevant with calf pneumonia infections *M. haemolytica*, *H. somni coronavirus, adenovirus* and Bovine syncytial virus (Autio et al., 2007; Hirose et al., 2003). Outbreak of bovine haemorrhagic septicaemia caused by *P. multocida* type B has been reported for first tinme by (Cuevas et al., 2020). Investigation of nontypical of *P. multocida* has been carried by (Sakmanoğlu et al., 2021) Surprisingly they found the nontypical strains number is higher than previously reported numbers. They found out of 92 isolates of *P. multocida* 34 are type A:3A as the most dominant strain type about (36.95%) all isolated were from animals with a respiratory disease which may imply to hidden role of nontypical *P. multocida* in pathogenesis too.

6.2. *Mannheimia haemolytica*

M. haemolytica in comparison with *P. multocida*; it tends to be moderate in severity with few numbers of diseases although recently an increase in annual incidence has been mentioned. In an epidemiological study conducted by (Biesheuvel et al., 2021) in Netherlands, morbidity rate reached 65% in dairy cows while in veal calves reached 20.6%. They attributed death in highly productive dairy cows to acute pleuropneumonia caused by *M. haemolytica*. This type of pneumonia results in death often within 24 hours. While in veal calves *M. haemolytica* infections cause fatal polyserositis, characterized by acute pleuritis, peritonitis, and pericarditis (Timsit et al., 2016). There are several serotypes of *M. haemolytica* Serotype 1 (S1) is most commonly isolated from diseased cattle or lesions of pneumonia while serotypes 2 and 6 are a common cause of sheep pneumonia (Klima et al., 2014). Serotype 6 is associated with BRD cases approximately 20% of the time or less. Whereas S2 is often isolated from the nasal passages in high concentration in healthy non-stressed cattle but infrequently may causes bovine pneumonia (Odendaal & Henton, 1995). *M. haemolytica* has been reported as the causative agent of mastitis in sheep with a prevalence rate reaching 40% in sporadic cases, this implies the significance of this bacterium in ovine mastitis some reports assume it may be similar to or even greater than that of classical agent of mastitis (*Staphylococcus aureus*) (Omaleki et al., 2011; Omaleki et al., 2016). Incidence rate of clinical mastitis is less than 5% in sheep and goats and increases to more than 20% in outbreaks associated with particular predisposing factors. *M. haemolytica* is also causing septicemia in young animals and pneumonia in animals at different ages. Reports of mastitis in sheep caused by saying *M. haemolytica* can be more transmitted horizontally transmission to lambs via suckling (Omaleki et al., 2016).

7. Diagnosis

P. multocida and *M. haemolytica* originated from the same family of Pasteurellaceae, both of them settle the upper and lower respiratory tract surfaces of an animal (Kisiela & Czuprynski, 2009). Moreover, diseases caused by them resemble each other so almost same diagnosis procedures are applied for them. The first step toward perfect diagnosis it is the isolation of the bacterium from the clinically ill animal through culturing on different media and later

identification through molecular methods (Dziva et al., 2008). Sampling depends upon disease type and whether a serological tests or culturing is going to be carried out for normal culturing usually samples like, lung, liver, spleen, kidney and intestine swaps from wounds also can be collected and cerebral fluids are useful if animal has septicemia. Prior to culturing, a direct examination can be conducted by creating an impression smear of the liver to observe bacteria under a microscope, using stains such as Giemsa or Wright's. Both Pasteurella and Mannheimia grow readily in trypticase soy, blood or dextrose agar plates at 35-37°C. *P. multocida* on blood agar plate usually is mucoid, 1 to 3 mm in diameter, and nonhemolytic colonies. Whereas *M. haemolytica* on blood agar plates is grey, medium sized colonies with zones of β-haemolysis (Carter & Cole Jr, 2012). As for serological tests serum and whole blood can be used. Serological approaches are mostly used for the assessment of herd immunity after vaccination campaigns in addition to research purposes. Routinely used tests are ELISA, disk diffusion test, rapid whole blood agglutination and serum plate agglutination. Moreover, indirect hemagglutination test (IHA) is considered the most serological test used for diagnosis of *M. haemolytica* infections and serotyping of field isolates (Carter & Cole Jr, 2012; WOAH, 2020). Also advanced techniques such as immunofluorescent microscope, in-situ hybridization (ISH) and polymerase chain reaction (PCR) are applied for more specific identifications (Townsend et al., 2001). They have developed multiplex PCR as a rapid alternative approach to the conventional capsular serotyping system of Henderson. Overall, PCR tests and molecular typing techniques have their benefits, they are most effective when used in combination with other methods and integrated into a broader investigative approach.

8. Transmission

Diseases caused by those pathogens are respiratory system restricted so the transmission of the infections from animal to animal or among birds easily occurs during Pasteurella and Mannheimia outbreaks. Chronically infected, asymptomatic carrier chickens or turkeys are considered to be the main sources of disease in fowl cholera infections this besides other carrier such as wild birds or other mammals (dogs, cats, and rodents). Fowl cholera infection does not seem to be vertical transmittable through the egg (Christensen et al., 2008). Generally, infections caused by *P. multocida* and *M. haemolytica* transimitted either by direct contact or from surrounding environment contaminated with coughing and excretions which could be nasal discharges, mouth saliva or lacrimation (D'Amico et al., 2022). These bacteria can survive long enough to be spread by contaminated water, feed, shoes, clothes and other equipment in the farms (Magyar & Lax, 2014). *M. haemolytica* in mastitis infection can be transmitted through milk secretions that contaminate the surrounding environment and to lambs through suckling, also infection can be transmitted ascendingly from lambs to dams if there are some abrasions or wounds on udder surface or teats (Kannangara et al., 2020; Omaleki et al., 2016).

9. Antibiotic Resistance

Antibiotic resistance by bacteria of an animal origin especially form animal raised for milk or meat consumption purposes shape a critical situation due to correlation with human health in general and possibility of new emergence of antibiotic resistant bacteria in human medicine field. Although not all *P. multocida* possess plasmids in some isolates plasmids with different sizes have been identified. Mostly these plasmids harbor resistance genes to multiple antibiotics (Hirsh et al., 1981; San Millan et al., 2011). Most commonly these resistance to antibiotics such as erythromycin, b-lactams, tetracycline, fluoroquinolones, novobiocin chloramphenicol, streptomycin, sulfonamides and thiamphenicol (Arif & Champlin, 1998). Generally antibiotic resistance plasmids of Pasteurellaceae members are transferrable among the family members (Bahr et al., 2021; San Millan et al., 2011; Shayegh et al., 2009). Studies carried by (Kadlec et al., 2011) and (Michael et al., 2012) showed that *P. multocida* strain 36950 isolated from a case of bovine respiratory disease (BRD), resist all antibiotics that commonly used to control BRD (Hirsh et al., 1981). Further genome sequencing of this isolate revealed that antibiotic resistance genes have been found on mobilizable or conjugative elements integrated into the chromosomes of the strain. Also studies showed increasing of antibiotic resistance by *M. haemolytica* to very high percentage of resistance to routinely used antibiotics, commonly *M. haemolytica* resist tilmicosin oxytetracycline, spectinomycin, erythromycin (McClary et al., 2011; Schink et al., 2022), Tetracycline and ampicillin. Obviously this wide range of resistance to different classes of antibiotics indicate that *M. haemolytica* is multidrug resistant; although the resistance is relative and differ according to region of research, and type of breeding system and feeding system and antibiotics usage status in the farms or feedlots, still ability of more antibiotic resistance emergence is high especially to antibiotics routinely used in BRD treatment (Ashrafi et al., 2022; Lubbers & Hanzlicek, 2013).

10. Prevention and control

Generally, respiratory diseases caused by and *P. multocida M. haemolytica* are preventable diseases; although its prevention may be a long and complicated process but is achievable. The process depends mainly on good management of the animal farms and good veterinary practice by veterinarians and assistant staff (Yeates, 2012). For treatment always antibiotics are the first choice to reduce the secondary infection and control animal parameters, Cephalothin of first-generation of cephalosporin and third-generation of cephalosporin antibiotics basically ceftiofur, both reported to be very effective (Nagai et al., 2019; Welsh et al., 2004). Oxytetracycline, streptomycin and rifampicin are found to be a good choice, also surgical treatment for atrophic rhinitis can be carried out (Lizarazo et al., 2006; Van Driessche et al., 2018).

Vaccination plays an important role in protection of livestock, poultry, and indirectly mankind, vaccine decreases incidence of diseases among herds of animals in endemic regions or areas of outbreaks. Since (Pasteur,1880) worked on a vaccine against fowl cholera causing *P. multocida* till today so many vaccine trials have been tried out and a lot of them succeeded in evoking the immune system with long term protection and marginal side effects, most of them are commercially available nowadays (Dabo et al., 2007; Elsayed et al., 2021). A wide range of vaccines have been introduced to control respiratory infections caused by these two-organisms starting from bacterins, live attenuated, killed, subunit, recombinant and DNA vaccines, each of these vaccines model has its specific features with different immune response produced by host animals (Ahmad, 2014; Wubet et al., 2019). In fowl cholera live attenuated vaccine has long cross-serotype protection when administered in food or water but it considers unsafe compared to bacterins which affords safety short-term, serotype-specific immunity (Chung et al., 2005). One of limitations in vaccination programs against *P. multocida* and *M. haemolytica* is multi-causative agent in bovine respiratory diseases and calf pneumonia, in these complex cases introducing one vaccine against specific causative agent is not enough for producing full protection, although some studies showed that vaccination with single vaccine may protect herds. In 1975 (Ismail et al., 2023; Thomson et al., 1975) found that vaccination of cattle with efficacious *M. haemolytica* vaccines prior to shipment potentially increased specific antibody titers and reduces shipping fever pneumonia. Also, control of respiratory disease in newborn calf may fail due to either failure of passive transfer of maternal antibodies through colostrum or due to unspecific immune repose from newborn calf which possesses native immune cells (Furman-Fratczak et al., 2011). In calf the most important cause of vaccination failure is the maternal antibodies which react against introduce vaccine and neutralize them so timing of vaccination is critical step. It should not be soon after birth not later after declining of maternal antibodies titers which may result in a period of vulnerability before newborn calf develop their own immune response (Detmer & Glenting, 2006; Tabatabaei et al., 2007). Therefore, measuring of maternal antibodies is very important before starting any vaccination program Moreover, using of unspecific adjuvant also can play vital role in failure of animal immunization (Roth, 1999). In addition, vaccination may fail due to so many reasons such as stress, malnutrition, concurrent illness and immunosuppression status which lead to imperfect immune response; also immaturity of immune system is one of these reasons. Vaccines also fail to evoke the immune system due to interference between multiple vaccine those introduced concurrently in last differences between vaccine strain and field strains should be considered when administrate vaccines (Adler et al., 1999; Harland & Potter, 1992; Mostaan et al., 2021).

11. Conclusion

Principles of one health must be applied in dealing with diseases caused by Pasteurella and Mannheimia in general. Moreover, the industry must potentially act with the diseases as an animal welfare issue not just a matter of profit and loss, and more importantly they should apply the experimentally approved to be an excellent choice of drug or vaccine. More specific research needed to shed light on phenotype and genotype differences among those organisms. Although a full genetic map has been successfully achieved still more genomic studies are needed to reveal the origin of virulence diversity, host specificity and predilection side of bacteria. Likewise developing an ideal vaccine against those bacteria also is one of future research challenges. According to available literature specifically some issues should be subjected to intensive investigations and research focus such as emerging and re-emerging infectious diseases and antigenic variants between agents. Evaluation of innate and adaptive immunity after infections or vaccinations is important for producing more specific drugs or vaccines in the future. Some vaccine strains have been in use for more than five decades so new innovative vaccines using new technologies are demanded. Lastly that shortage in diagnostic field tests is also one of the challenges faces scientists nowadays.

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