*Open Veterinary Journal*, (2025), Vol. 15(2): 519-532
ISSN: 2226-4485 (Print)
ISSN: 2218-6050 (Online)

*Review Article*
DOI: *10.5455/OVJ.2025.v15.i2.3*

Submitted: 28/10/2024 Accepted: 21/01/2025 Published: 28/02/2025

# Hemorrhagic septicemia: A major threat to livestock health

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**ABSTRACT**
Hemorrhagic septicemia (HS) is an acute septicemic disease that primarily affects cattle and buffalo. This illness is caused by a specific serotype of Gram-negative coccobacillus, *Pasteurella multocida*. The frequency and distribution of HS epidemics involving various animal species vary according to the agroclimatic zone. HS has significant economic implications, particularly in Asia and, to a lesser extent, Africa. The transmission of HS can occur through direct contact, ingestion, or inhalation of contaminated feed or water. The virulence factors of *P. multocida* include a number of defense mechanisms or components that help the pathogen be detected by the host immune system. A number of components contribute to the pathogenicity of *P. multocida*, particularly its toxins and capsules. The primary clinical signs and peracute or acute pathological alterations in other HS cases include septic pneumonia, petechial hemorrhages, ecchymoses in the serous membranes, adrenal glands, and abomasum with severe bleeding, as well as widespread head and neck edema. Affected animals exhibit fever, sadness, and other vague clinical symptoms (such as reduced milk production), which are quickly followed by copious serous nasal discharge and excessive salivation. HS-causing *P. multocida* strains may not be found in previously obtained samples, but they can be cultivated from blood during the later stages of the illness. Antibiotics of several types have been used to treat HS. Effective control of various HS diseases will be aided by hygienic planning, immunoprophylaxis, chemotherapy, and fundamental management practices, including feeding and maintenance.
**Keywords:** Hemorrhagic septicemia, Livestock, *Pasteurella multocida*.

## Introduction

Hemorrhagic septicemia (HS) is an acute septicemic disease that primarily affects cattle and buffalo. It is highly fatal and causes significant morbidity and mortality rates in the livestock industry, particularly in Asian and African nations (Shome *et al*., 2024). This illness is caused by a particular serotype of the Gram-negative coccobacillus *Pasteurella multocida*, which primarily coexists in the nasopharynxes of animals as a commensal (Shivachandra *et al*., 2011). Various *P.*

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*multocida* serotypes are linked to a group of illnesses collectively referred to as "pasteurellosis". Frequently, *P. multocida* functions in tandem with other bacterial, viral, or parasitic illnesses or plays a supporting role in the pathophysiology of the disease (Wilson and Ho, 2013).

The Office International des Epizooties classified HS as a Schedule B disease because it is associated with primary pasteurellosis outbreaks with a 100% mortality rate in infected animals in endemic areas of Africa and Asia (Almoheer *et al*., 2022). This illness has a high global index and limits the health of animals for underprivileged farmers. However, HS is a primary pasteurellosis that can only be propagated in susceptible host species using pure cultures of the causative agent (Hasnan *et al*., 2022). This is similar to certain strains of *Salmonella* that induce a particular form of salmonellosis in a host species, such as typhoid fever.

Buffaloes have a more severe form of the disease with clear clinical indications, making them generally more vulnerable to HS than cattle (Horadagoda *et al*., 2001). Furthermore, reports or suspicions have indicated the presence of *P. multocida* in Bali cattle (Besung *et al*., 2016), camels (Kasivalu *et al*., 2022), pigs (Kim *et al*., 2019), donkeys (Abdulkadir *et al*., 2024), goats (Tabatabaei and Abdolahi, 2023), sheep (Nguyen *et al*., 2023), yaks (Jia *et al*., 2023), horses (Fitrah *et al*., 2013), and poultry (Handijatno *et al*., 2019). Unhealthy farming circumstances are more likely to cause this disease. The clinical signs of HS include submandibular enlargement together with fever, appetite loss, nasal discharge, increased saliva production, and trouble breathing (Almoheer *et al*., 2022). Clinical symptoms typically appear quickly over several hours to days. Recoveries are rare because the sickness is brief and only a small number of animals can receive timely treatment.

Several areas of Asia, Africa, the Middle-East, and Southern Europe are included in the geographical distribution of HS (Shivachandra *et al*., 2011). Its distribution is influenced by livestock methods, animal species kept, and climate. Due to the abundance of cattle and buffaloes in Asia, which are necessary for milk production and draft power, this disease has significant economic implications. The fact that there are fewer cattle and buffaloes in Africa and that other animal diseases result in less significant financial losses also make this disease less significant there (Benkirane and De Alwis, 2002). In endemic places, outbreaks are more likely to occur during the rainy season, when the organism can spread more readily, and young animals are more vulnerable to sickness (Chanda *et al*., 2024). Across environments where animals lack immunity, serious illness is common among all age groups (Almoheer *et al*., 2022).

Animal owners are typically terrified of HS because it is known to be a problem in the livestock business. The purpose of this review is to explain the etiology, history, epidemiology, pathogenesis, virulence factors, pathology, clinical symptoms, diagnosis, differential diagnosis, transmission, economic impact, zoonotic potential, treatment, vaccination, and control of HS. Thus, this study significantly contributes to the existing understanding of HS and raises public and professional veterinary awareness of the risks associated with HS illness and the significance of prompt diagnosis and treatment.

***Etiology***

Based on the Carter–Heddleston classification system, classical HS is caused by the *P. multocida* serotypes B:2 and E:2. This classification also corresponds to serotypes 6:B and 6:E of the Namioka-Carter classification system (Ahmed *et al*., 2014; Tawab *et al*., 2020).

Depending on the growth stage, *P. multocida* cells are pleomorphic, tiny, and nonmotile. They can be found alone, in pairs, or in short chains (Wilson and Ho, 2013). The organism does not produce endospores and is Gram-negative.

This organism has both fermentative and oxidative metabolic types and is mesophilic and chemo-organotropic (Richardson *et al*., 2023). The last electron acceptor, molecular oxygen, can be replaced by fumarate and nitrate. Although some species and strains require factor-V, the majority of species are not dependent on factor-X (protohemin or protoporphyrin IX) or factor-V (beta-nicotinamide adenine dinucleotide) (Vu-Khac *et al*., 2020). It is generally known that *P. multocida* strains from cattle, poultry, goats, leporinus, and sheep exhibit phenotypic diversity (Stahel *et al*., 2009). Studies on *P. multocida* infections through epidemiology have revealed the value of biochemical reactions. Variations in the carbohydrate fermentation reactions of the isolates could be caused by host stress, environmental variables influencing enzyme profiles, and the indiscriminate use of chemotherapeutic drugs in specific geographic locations (Hanchanachai *et al*., 2021).

The molecular weight of the Pasteurella genome ranges from $1.4 \times 10^9$ to $1.9\ 10^9$, and its G+C content ranges from 37.7 to 45.9 mol% (Peng *et al*., 2019). The whole genome sequence of a common avian clone of *P. multocida*, Pm70 (serotype A:3), which causes chicken cholera, has been completed. However, no attempt has been made to sequence the genomes of the *P. multocida* strains implicated in the pathogenesis of HS to date (May *et al*., 2001). The organism possesses a single 2,257,487-bp circular chromosome with six ribosomal RNA operons, 5b 7 tRNAs, and 2014 projected coding areas (Bosch *et al*., 2004; Peng *et al*., 2019; Mahboob *et al*., 2023). The whole sequence covered 89% of the chromosome and identified 2014 possible CDs with an average size of 998 bp (May *et al*., 2001; Peng *et al*., 2019; Mahboob *et al*., 2023). Based on pairwise comparisons of 1,197 orthologous sequences,

a genome-scale evolutionary study indicated that the γ subdivision of proteobacteria diverged approximately 680 million years ago, whereas *P. multocida* and *H. influenzae* separated approximately 270 million years ago (Peng *et al*., 2016).

***History***

This organism's history started in 1782 when Chabert conducted the first study of it in France. Later, in 1878–1879, Revolta and Revolee described the bacterium. Bollinger described sickness in buffalo and cattle during the same period. Trevisan suggested the name "*Pasteurella*" in 1887 to honor Louis Pasteur's groundbreaking research on the etiology of poultry cholera conducted in the early 1880s (Cavaillon and Legout, 2022). In 1939, Rosenbach and Merchant proposed the term "*P. multocida*" (multocida—killing many, referring to pathogenicity to many species), which was a change from the original name of the bacterium, which was called after the host species in which it causes disease (cattle, boviseptica) (Shivachandra *et al*., 2011). There are four subspecies of this species: *P. multocida* subsp. *multocida*, *P. multocida* subsp. *septica*, *P. multocida* subsp. *gallicida*, and *P. multocida* subsp. *tigris* (Duan *et al*., 2024). *P. multocida* is a member of the large family *Pasteurellaceae*, which consists of 15 genera with three core genera: *Pasteurella*, *Actinobacillus*, and *Haemophilus* (Wilson and Ho, 2013). These organisms are commensals or obligatory parasites of vertebrates that primarily colonize the mucosal surfaces of the oropharynx, upper respiratory tract, and other parts (Harper and Boyce, 2017).

Numerous researchers have developed a serotype classification associated with specific illness presentations. Four immunological typing classes (I, II, III, and IV) were identified by Roberts in 1947 using a system based on the passive antiserum protection of mice. Hudson introduced the V-type in 1954. Namioka and Murata identified 11 serotypes (1–11) using the tube agglutination test in 1961 (Seo *et al*., 2009). The most popular and widely used serotyping system currently is a combination of Heddleston somatic typing and Carter capsular typing, which identifies 16 (1–16) somatic serotypes based on agar gel precipitation and five capsular serogroups (A, B, D, E, and F) based on the indirect hemagglutination (IHA) test (Tang *et al*., 2009). Numerous classifications have been used to identify the causal agents of HS, including Namioka and Carter types 6:B and 6:E, Heddleston type 2, Roberts type-I, and Carter type B (Ahmed *et al*., 2014). According to the Carter–Heddleston system, the Asian serotype for HS is B:2, and the African serotype is E:2, which correlates to 6:B and 6:E in the Namioka–Carter method (Tawab *et al*., 2020).

***Epidemiology***

The frequency and distribution of HS epidemics involving various animal species vary according to the agroclimatic zone. Regardless of the season, disease outbreaks occur all year round. This is contrary to the belief that the disease primarily strikes during or after the rainy season. In India, the frequency of disease outbreaks varies greatly between states and within each state from year to year (Chanda *et al*., 2024). The condition is less common in developed nations, but HS has been documented in the majority of the world's nations, particularly in developing and impoverished nations in Asia and Africa (Shivachandra *et al*., 2011). HS has been reported throughout Southern Europe and the Middle East (Shome *et al*., 2019; Habib *et al*., 2019; Sting *et al*., 2020).

In Malaysia, the first HS report was made in 1900 (Thomas, 1972). From 1994 to 2005, 48 outbreaks were recorded. Almost every year except for 2004, outbreaks have occurred. The period from 1995 to 2000 saw the most outbreaks. The HS epidemic peaked during the 2000 Nipah virus outbreak. All isolates from the Malaysian outbreak were determined to be *P. multocida* serotype B:2, whereas the states of Perlis, Selangor, and Johor had not experienced any HS outbreaks in the previous 12 years; Pahang, Terengganu, Kelantan, and Perak had between 8 and 11 outbreaks. A case of HS illness was recorded in Pasir Mas, Kelantan, in February 2006, which led to the discovery of 77 dead buffaloes (Zamri-Saad and Annas, 2016).

Furthermore, it has been reported that HS accounts for 45%–55% of all cattle mortality in India during the past 40 years. Approximately five million animals in India are said to perish from HS illness each year as a result of the present vaccine's inability to offer long-term protection (Bardhan *et al*., 2020). Similarly, buffalo calves have been reported to account for 31.48% of all deaths in Pakistan and 34.4% of all deaths in susceptible livestock (Habib *et al*., 2019). Furthermore, a study by Farooq *et al*. (2011) found that among 10 infected/outbreak-affected villages in Pakistan with a total population of 4248 animals, the overall morbidity, mortality, and case fatality rates were 17.39%, 14.66%, and 84.30%, respectively. Additionally, it is said that HS is a common disease in India and is more common in areas with subpar agricultural circumstances (Shome *et al*., 2024). In this case, a comprehensive free-range agricultural method is used to raise the animals. These circumstances create the perfect setting for the propagation of HS.

HS outbreaks in cattle and buffaloes in Asia can present as serious illnesses (Benkirane and De Alwis 2002). Three factors are considered important for epidemiology: (1) high temperature and moisture content of the climate; (2) poor dairy practices, such as a lack of fodder, strain on animals, and crowded, dirty farmlands; and (3) certain animal species are less tolerant. According to Karunasree (2016), buffaloes and calves are more vulnerable to this disease than cattle. Numerous nations, including Zimbabwe (Lane *et al*., 1992), Sri Lanka (De Alwis and Vipulasiri, 1980), the Middle East, Africa, and Pakistan (Khan

*et al*., 2006; Farooq *et al*., 2007), have reported HS outbreaks. An extensive mortality rate of 5%–90% has been described in various epidemic reports in India and the Philippines.

According to Khan (2012), from mid-November to mid-December 2010, a significant HS outbreak occurred in Greater Cholistan's dromedary camel population. Although HS is regarded as one of the five major camel diseases and results ithat resultnt financial losses, *P. multocida* is not a frequent infection of the respiratory tract in dromedary camels. Acute septicemia outbreaks in cattle in New Zealand typically have a high mortality rate, with anthrax and HS serving as the primary exotic differential diagnosis (Jauregui *et al*., 2023). In undeveloped populations, HS epidemics affect cattle of all ages and frequently lead to 100% fatality.

***Pathogenesis***

The tonsil region is thought to be the first site of multiplication for the *Pasteurella* organism once it has entered the animal at the beginning of its pathogenic process (Wilson and Ho, 2013). This infection result is determined by the interplay between the host animal's unique immune system and nonspecific resistance variables, on the one hand, and the organism's virulence and rate of reproduction *in vivo*, on the other (Lin *et al*., 2022). Thus, the infectious dosage is crucial, and clinical disease can develop if the organism manages to overcome the host's defenses. The animal becomes an immune carrier if defensive mechanisms take over the body, a condition known as a "stalled infection". Strong immunity is possessed by these animals, and "herd immunity" results from a large number of immune animals following a disease epidemic (Abedon, 2017).

There is currently no evidence that strains of *P. multocida* that cause HS generate exotoxins. Nevertheless, it has been noted that hyaluronidase is produced by serotype B:2 bacteria that cause HS, although certain B:2 strains that are not linked to HS do not generate this enzyme (Bosch *et al*., 2004). Hyaluronidase is also not produced by other type B strains, such as B:3 and B:4, which are known to generate a condition identical to typical HS (Kumar *et al*., 2004). Consequently, it is unclear whether this enzyme plays any role in pathogenesis.

It is noteworthy that certain strains of type B (B:2) and type E (E:2) exhibit reliable experimental reproduction of the disease (Mostaan *et al*., 2020). Although pathogenicity has not always been proven experimentally, other type B strains (B:3,4, B:1, and B:4) have been linked to occasional disease outbreaks (Orynbayev *et al*., 2019). Whether the early strains had particular virulence characteristics and, if so, whether they were based on genetics or phenotypic traits is still unknown. Regardless of the virulence factors, it is logical to infer that they allow the organism to multiply in spite of the body's defenses, leading to the development of disease-specific lesions (Ferreira *et al*., 2015a).

The classical Asian serotype (B:2) has been shown to have the ability to vacuolate macrophages and ultimately lyse them, which would decrease phagocytosis and encourage the growth of invasive bacteria (Kachooei *et al*., 2017). *In vitro* investigations using a mouse macrophage cell line and a model using mouse peritoneal macrophages have shown that cytoplasmic vacuolating activity causes macrophage lysis and mortality in HS-causing type B strains but not in non-HS B strains (Praveena *et al*., 2010). Although not observed for non-HS strains, this activity was also observed in culture supernatants from the same strains (Steen *et al*., 2010). It is expected that free endotoxins, which are also present in other Gram-negative bacteria, would be present in the culture supernatant in the absence of exotoxins.

***Virulence factors***

The virulence factors of *P. multocida* include a number of defense mechanisms or components that help the pathogen be detected by the host immune system. A number of components contribute to *P. multocida* pathogenicity, particularly its toxins and capsules.

***Capsule***

The virulence of *P. multocida* has been linked to capsules (Furian *et al*., 2014). The B2 capsule biosynthesis locus of *P. multocida* was identified and its nucleotide sequence was determined by Boyce and Adler (2000). Intraperitoneal challenge infection in mice was used to investigate the virulence of wild-type, mutant, and complemented strains; the presence of the capsule was found to be a significant factor in virulence.

***Endotoxin***

The toxigenic effects of *P. multocida* have been successfully studied using endotoxin generation in vero and embryonic lung cells (Wilson and Ho, 2013). The toxigenic effects of experimental animal species vary widely. Rabbits are more susceptible to the deadly effects of soluble and heat-stable toxins from bovine and avian strains than rats. After being intravenously administered to cattle and buffalo in an experiment, the pure *P. multocida* type 1 toxins were discovered to induce fever, bloody diarrhea, and malaise (Kubatzky, 2022). Toxins generated by certain *P. multocida* strains have generally been implicated in naturally occurring events in calves, sheep, and pigs (Lainson *et al*., 2002; Bernal *et al*., 2022; Cao *et al*., 2024; ). According to Massacci *et al*. (2018) and Yuan *et al*. (2024), the toxins caused dermonecrotic effects in rabbits and guinea pigs. *P. multocida* also has a cytopathic impact, which is a harmful decrease in DNA synthesis, particularly in cells that divide quickly (Wilson and Ho, 2013). Along with the protein fraction, *P. multocida*'s toxigenic qualities are linked to structural elements of the cell membrane, including the endotoxin fraction lipopolysaccharide (LPS) (Harper *et al*., 2013). In addition to its immunogenic qualities, the *P. multocida* LPS-protein complex possesses several gram-negative bacterial endotoxins.

***Enzymes***

There are several enzymes that *P. multocida* generates. The members of serogroup A, B, D, and E produce neuraminidase (Straus *et al*., 1996). The strains belonging to serogroups A and Debye exhibited the highest levels of activity. Antisera against serogroup A, B, D, and E inhibit type D activity, but homologous antiserum exclusively inhibits type E activity (Harper *et al*., 2017).

It is well known that serotype B:2 associated with HS produces hyaluronidase and chondroitinase (Rimler and Rhoades, 1994). The enzyme hyaluronidase is typically linked to invasive mechanisms in worms, snake venom, and bacteria (de França and Tambourgi, 2023). The bovine and deer B:3,4 strains are examples of type B strains that do not manufacture hyaluronidase because they include additional somatic antigens (Shivachandra *et al*., 2011). Despite the conclusion that hyaluronidase production is a trait exclusive to serotype B:2 strains that cause HS, Almoheer *et al*. (2022) reported a B:2 mutant that generated hyaluronidase but was non-virulent for cattle and buffalo and had low virulence for mice and rabbits. The capacity to manufacture hyaluronidase or other enzymes is not clearly linked to virulence.

***Antigens***

*Pasteurella multocida* shares antigens with other Gram-negative bacteria that are closely related. There have been reports of antigenic associations with *Neisseria catarrhalis*, *Haemophilus canis*, *Actinobacillus lignieresi*, *P. haemolytica*, *Haemophilus influenzae*, *Escherichia coli*, and *Yersinia paratuberculosis* (Peng *et al*., 2019). An investigation of 11 *P. multocida* isolates from cases of HS, bovine pneumonia, and chicken cholera that belonged to various serotypes revealed the presence of cross-protection (Mahboob *et al*., 2023). It was discovered that avian cholera strains and serotype A:5 strains provide defense against several other strains, irrespective of the illness they cause (Davies *et al*., 2003). Antigen components with a molecular weight between 20 and 120 kDa are linked to this protection.

***Plasmids***

Plasmids from *P. multocida* strains of different animal species have been shown to range in size from 1.3 to 100 kb, with the majority being between 2 and 6 kb (El-Demerdash *et al*., 2023). These plasmids encode different virulence traits, like as poisons, or provide resistance to antibiotics. Plasmid profiles are considered both virulence markers for *P. multocida* and crucial epidemiological tools for distinguishing between strains that share a common phenotype (Vu-Khac *et al*., 2020). Despite being nonconjugative, several of the identified R plasmids were easily transformed into *P. multocida* and *Escherichia coli* (Zhao *et al*., 2021).

***Pathology***

Following experimental injection, postmortem abnormalities included minor petechial hemorrhages in the heart and swollen lungs (Shivachandra *et al*., 2011). Acute examples include pericarditis with serous hemorrhage in the left ventricle, edematous lymph nodes, inflamed and grayish-red lobular lungs, blood-stained exudate, and extensive hemorrhages on the pleural surface and parenchymal organs (Chanda *et al*., 2024). The primary clinical signs and peracute or acute pathological alterations in other HS cases include septic pneumonia, petechial hemorrhages, ecchymoses in the serous membranes, adrenal glands, and abomasum with severe bleeding, as well as widespread head and neck edema (Doyle-Baker *et al*., 2020). Common conditions include rhinitis and necrotic pharyngeal mucosa. The nasal and pharyngeal mucosa have the most severe histological lesions (Eriksen *et al*., 1999). Diffuse cellulitis in the subcutaneous and intermuscular tissues causes swelling of the head and neck (De Alwis, 1992). Large numbers of bacteria in the pulmonary capillaries are the first lesions in the lungs, but there are also often different levels of fibrinous exudation in the alveoli and neutrophil infiltration (Lomas-Neira *et al*., 2006).

***Clinical symptoms***

HS can be either acute or peracute. Most HS cases are peracute, with mortality occurring within 24 hours (Almoheer *et al*., 2022). Most clinical cases have been reported in buffalo and cattle. Buffalo typically exhibits a more severe shorter and quicker disease, although the two species have comparable symptoms (Hasnan *et al*., 2022). The affected animals exhibit fever, sadness, and other vague clinical symptoms (such as reduced milk production), which are quickly followed by copious serous nasal discharge and excessive salivation (Doyle-Baker *et al*., 2020). Longer animal lifespan may result in mucopurulent nasal discharge. Other distinctive symptoms include edematous swelling in the submandibular area and dyspnea, which may be followed by frothing in the mouth or nostrils (Kutzer *et al*., 2021). The front legs may occasionally get swollen, along with the neck and chest. Some animals may suffer from hemorrhagic gastroenteritis, which is characterized by diarrhea and abdominal pain (Dupont *et al*., 2021). At necropsy, the brains of certain cattle and buffalo exhibit signs of meningitis or hemorrhagic encephalitis, despite the fact that neurological signals appear to be absent in most cases (Shome *et al*., 2024). HS typically causes an animal to collapse and die a few hours to days after the illness first appears (Almoheer *et al*., 2022). It is also possible to experience sudden death with minimal or no clinical symptoms. In particular, buffalo rarely recover from symptoms. HS symptoms are similar in other species; however, some pigs exhibit neurologic symptoms (such as tetraparesis or opisthotonus), and surviving pigs occasionally exhibit discolored and necrotic skin sores on their neck, throat, or lower belly (Peng *et al*., 2018). Some experimentally infected goats did not exhibit the typical subcutaneous edema, but they did exhibit other symptoms typical of HS (Mushtaq *et al*., 2022). In

certain wild ruminants with septicemic pasteurellosis, comparable clinical symptoms have been observed (Malhi *et al*., 2016).

***Diagnosis***

HS-causing *P. multocida* strains may not be found in previously obtained samples, but they can be cultivated from blood during the later stages of the illness (Fegan *et al*., 2024). This organism is not always present in bodily fluids or nasal secretions, but it can occasionally be detected in these fluids (Wilson and Ho, 2013). Since they are typically discovered on nonselective media like blood agar, obtaining a fresh sample free of contaminating bacteria, including post-mortem intruders, increases the likelihood that the culture will be successful (Narcana *et al*., 2020). After incubation for 24 h at 37°C, surface colonies on sheep blood agar plates were smooth, spherical, shiny, grayish or yellowish, nonhemolytic, and 1-2 mm in diameter (Piorunek *et al*., 2023). The type of capsule and level of encapsulation determine colony size. In rich broth, good growth was obtained; on MacConkey agar, no growth was observed (Desem *et al*., 2023). The organism exhibits bipolar staining with Leishman, methylene blue, or Giemsa staining in fresh cultures, blood smears, exudates, and tissues of infected animals (Panna *et al*., 2015). Oxidase, alkaline phosphatase, and catalase tests were positive (Massacci *et al*., 2018). Sugars such as mannose, glucose, galactose, sucrose, L-sorbose, fructose, m-inositol, rhamnose, and adonitol are all metabolized by this organism (May *et al*., 2001). *P. multocida* is not able to hydrolyze aesculin, salicin, or starch. All lysine decarboxylase, urease, gelatin liquefaction, and arginine dihydrolase tests were negative (Gerardo *et al*., 2001).

The bacteria can frequently grow from blood samples or heart swabs obtained within hours of death during necropsy (Rawat *et al*., 2019). It is also possible to sample other visceral organs. The last organs to be cleared of impurities after death are the brain and spleen. Long bones devoid of tissue may contain *P. multocida* if the animal has been dead for an extended length of time; the bone marrow is cultured following surface sterilization (von Schroeder and Bell, 1996).

*Pasteurella multocida* is a small, oval, Gram-negative rod that exhibits bipolar staining in blood or tissue smears. Leishman, Giemsa, or methylene blue staining makes bipolar staining more visible (Panna *et al*., 2015). Culturing the *P. multocida* strain linked to HS from an infected animal is often a method for a conclusive diagnosis is achieved (Fegan *et al*., 2024). Although a variety of different media, such as casein/sucrose/yeast agar with 5% blood and starch dextrose agar, can also be utilized, this organism thrives on blood or chocolate agar (Varshney *et al*., 2020). Colonies can be identified by the polymerase chain reaction (PCR), biochemical, and serological tests (Lichtensteiger *et al*., 1996). Bipolar labeling may be removed with serial passage, and pleomorphism is expected when analyzing bacterial morphology, particularly in older cultures (Wilson and Ho, 2013; Fuller *et al*., 2020).

The agglutination test for somatic type determination, the rapid slide agglutination test or IHA test for capsular type determination, agar gel immunodiffusion for capsular and somatic type determination, and counter-immunoelectrophoresis for quick identification of B and E capsular types are among the serological tests used for serotyping (Abed *et al*., 2020). It may be challenging to type some isolates using this technique. Some laboratories use genetically based serotyping technologies, such as PCR-based procedures (Peng *et al*., 2019). Although they are typically only available in research labs, genetic techniques like multilocus sequencing and pulsed-field gel electrophoresis, might further characterize isolates for epidemiological investigations (Oh *et al*., 2019).

Additionally, serotypes associated with HS can be identified directly in clinical samples using PCR techniques (Townsend *et al*., 1998). There are documented tests for loop-mediated isothermal amplification. If *in vitro* culture fails, especially if the corpse is polluted, *P. multocida* can be isolated by inoculating animals, such as mice, with the *P. multocida* pathogen (Bhimani *et al*., 2015). However, for animal welfare reasons, it is best to avoid inoculating animals if possible.

Serological studies are typically ineffective for diagnosing clinically afflicted animals because they typically pass away quickly before generating antibodies (Orynbayev *et al*., 2019). However, serology is occasionally used for retrospective diagnosis. It is recommended to use high titers in surviving or contact animals (1:160 or higher by IHA) (Dogra *et al*., 2015). For a number of species, ELISAs for the detection of antibodies have also been developed (Singhla *et al*., 2020). The primary application of immunohistochemistry for antigen detection is research (Pors *et al*., 2013).

***Differential diagnosis***

In the area where it is recorded, HS must be distinguished from other illnesses that have comparable symptoms. Other illnesses that can cause sudden death, such as rinderpest, anthrax, and black quarters, should be considered if the situation is acute and marked by sudden death (Mondal and Yamage, 2014). Non-infectious causes of sudden mortality, like acute poisoning, lightning, and snakebite, are equally significant. It is necessary to differentiate the respiratory-dominated longer syndrome from other types of pasteurelloses caused by *P. haemolytica* or serotypes other than groups B and E (Abera and Mossie, 2022). It is important to keep in mind that fatal septicemia is a consistent hallmark of both chronic and subacute forms of HS pneumonia, even though this may not be the case for other serotypes.

***Transmission***

The transmission of HS can occur through direct contact, ingestion, or inhalation of contaminated feed or water (Kutzer *et al*., 2021). Although they can also be found in other secretions and excretions, such as urine and feces, pathogenic organisms are believed to be mostly transmitted through respiratory secretions (Mushtaq *et al*., 2022). Some infected animals develop into carriers, keeping *P. multocida* in upper respiratory tract lymphatic tissues (such as the tonsils) and occasionally excreting it in nasal secretions (Wilson and Ho, 2013). Stress might cause release.

Six weeks after inoculation, one study discovered nucleic acid in the lungs, reticulum, ileum, and ureters of experimentally infected buffalo calves; however, corticosteroid treatment did not cause shedding from these areas after 15–17 days (Praveena *et al*., 2014). Immediately following an outbreak, *P. multocida* carriage in cattle and buffalo seems to be at its highest: up to 20% of surviving animals may be carriers for a while, but this is believed to drop to 5% or less after six months (Dabo *et al*., 2007).

*P. multocida* can live for hours or even days in wet soil or water, but not for extended periods of time in the environment (Thomson *et al*., 1992). Transmission is facilitated by high humidity and rainy weather (Abdulkadir *et al*., 2024). The epidemiology of this disease is not significantly affected by biting arthropods.

***Economic impact***

HS has significant economic implications, particularly in Asia and, to a lesser extent, Africa and the Middle-East (Almoheer *et al*., 2022)**.** There are 432 million cattle and 146 million buffaloes in Asia, which make up 30% and 95% of the global cow and buffalo populations, respectively, and are considered vulnerable animals (Farooq *et al*., 2011). The most vulnerable buffaloes provide over half of the milk produced in India, the country with the largest milk production in Asia (Shome *et al*., 2024). The buffalo account for 37% of all milk output in Asia. Since rice is a staple diet in many nations, most cattle and buffalo are used as draft animals in rice fields (Benkirane and De Alwis, 2002). The significance of economic losses resulting from HS is thus demonstrated by the large number of buffaloes in Asia, their high sensitivity to the disease, and the high case fatality rate. The estimated annual economic losses for the livestock industry is USD 792 million per year (Shome *et al*., 2019). In Pakistan and India, economic losses, especially from bovine deaths, were estimated to be approximately USD 1.15 billion (Michael *et al*., 2021).

Measuring losses from HS has only been undertaken in a small number of nations, and the approaches used vary widely (Hodgson *et al*., 2005). As a result, although this research will reveal trends, it is not entirely comparable. Passive reporting systems provide the majority of the information currently available.

It has been determined that HS is responsible for 46%–55% of all cow mortality in India during the past 40 years. Foot and mouth disease (FMD), rinderpest, blackquarter, anthrax, and HS were the five endemic diseases that killed the most people during the 12-year period from 1974 to 1986, accounting for 58.7% of all deaths (Kumar *et al*., 2004). Approximately 15% of buffaloes and 8% of cattle in HS-endemic areas perished from HS annually in the 1970s, according to an active monitoring study conducted in Sri Lanka. Only 1,200 to 1,500 deaths annually were reported by the passive reporting system among the roughly 2.5 million heads of cattle and buffalo (Hettiarachchi *et al*., 2012).

Additionally, HS is ranked as the most economically significant bacterial or infectious disease in other South Asian countries. According to reports, HS was responsible for 34.4% of all susceptible animal deaths in Pakistan. An estimated 1.89 billion rupees (350 million USD) are lost economically each year due to the 17.7 and 18.8 million cow and buffalo populations, respectively (Moustafa *et al*., 2013). HS is an economically significant disease affecting cattle and buffalo in Southeast Asia, including Indonesia, Thailand, the Philippines, Laos, Cambodia, Myanmar, and Malaysia (Benkirane and De Alwis, 2002). In Cambodia, HS is the focus of 50% of government initiatives to control livestock diseases (Kawasaki *et al*., 2015). Estimates of livestock losses from HS in Malaysia, a country with a comparatively small population of 735,000 cattle and 186,000 buffaloes, are RM2.25 million (USD 0.85 million) (Bisht *et al*., 2006).

***Zoonotic potential***

Human infection with *P. multocida* serotypes B:2 or E:2 has not been documented, and animal HS epidemics have not been linked to human illness. In humans, *P. multocida* is an opportunistic infection; hence, care should be taken to prevent unnecessary exposure (Ferreira *et al*., 2015b). Even though soft tissue infections are the most frequent cause of these diseases, they can also occasionally be linked to other illnesses, such as osteomyelitis, endocarditis, meningitis, respiratory infections, or septicemia, particularly in immunocompromised individuals or those with underlying medical disorders (Malek *et al*., 2019). Numerous human diseases have been linked to serogroups A and D; nevertheless, in the majority of these cases, the causative organism's serotype remains unknown (Piorunek *et al*., 2023).

***Treatment***

Antibiotics of several kinds have been used to treat HS illness. *P. multocida* can be effectively treated with antibiotics such as penicillin, florfenicol, amoxicillin, erythromycin, spectinomycin, cephalothin, tetracycline, ceftiofur, cefquinome, enrofloxacin, streptomycin, gentamicin, trimethoprim/sulfamethoxazole,

sulfonamides, tilmicinocin, and norfloxacin (Kerek *et al*., 2024).

Ferreira *et al*. (2012) added that several antibiotics are typically used to treat *P. multocida* infections. Antimicrobial susceptibility of *P. multocida* isolates from HS revealed that fluoroquinolones, tetracyclines, florfenicol, and cephalosporins were the most effective antimicrobials. Numerous studies conducted in France, Malaysia, and Japan have reported similar findings (Itoh and Kurai, 2018; Sabsabia *et al*., 2021; Pintér *et al*., 2024). Additionally, isolates of *P. multocida* have been found to have high levels of resistance to cotrimoxazole and sulfonamides (Petrocchi-Rilo *et al*., 2018).

In addition, Naz *et al*. (2012) used the antibiogram test to screen sixteen *P. multocida* isolates in the field against 15 different antibiotics. The results showed that 87.5% of isolates were sensitive to ofloxacin, gentamicin, enrofloxacin, and ciprofloxacin, followed by 81.25% to amikacin and norfloxacin, and 75% to kanamycin. Tetracycline was susceptible to 56.25% of isolates, whereas doxycycline, vancomycin, and chloramphenicol were susceptible to 50% of isolates. Sulfadiazine was least susceptible (12.5%), whereas 25% of the isolates were susceptible to erythromycin. In addition, 50% of the isolates in this investigation were found to be resistant to erythromycin and sulfadiazine. Likewise, ofloxacin, amoxicillin, cotrimoxazole, ceftiofur, augmentin, norfloxacin, aztreonam, gentamicin, and cephalexin were used in antibiotic susceptibility testing (Jabeen *et al*., 2013). *P. multocida* was shown to be responsive to gentamicin and ceftiofur, more vulnerable to amoxicillin and aztreonam, and resistant to augmentin and cotrimoxazole. HS has been treated with antibiotics. However, long-term careless antibiotic use has led to the development of resistant organisms, including multidrug-resistant (MDR) *P. multocida* (Oh *et al*., 2018). P. *multocida* is primarily resistant to cotrimoxazole and sulfonamides (Schwarz *et al*., 2007).

***Vaccination***

HS vaccines are either solid bacterins with adjuvants or simple bacterins destroyed with formalin (Hodgson *et al*., 2005). Adjuvants raise immunity levels and extend its longevity (Facciolà *et al*., 2022). Encapsulated germ cells must be present in the cultures used to produce vaccines. Three vaccines have been used to prevent HS: oil adjuvant vaccine (OAV), precipitated aluminum hydroxide vaccine (APV), and bacteria (Kumar *et al*., 2015). Repeated vaccination is required to provide adequate immunity to bacteria. The possibility of a shock reaction, which is rare in APV and virtually nonexistent in OAV, exists when solid bacterin is administered. This vaccine is standardized using a turbidity test to determine its bacterial density. Mice are the simplest test to perform. For primary vaccination, 4–6 months is the recommended age (Muenthaisong *et al*., 2020). A vaccination protocol of one OAV dose at 4–6 months of age, one booster dose at 3–6 months later, and yearly revaccination after that is advised for routine prophylactic vaccination. It is recommended that vaccinated animals receive one dose of APV and then one dose of OAV in the event of an outbreak (Verma and Jaiswal, 1998). Annual HS vaccinations are administered in Sudan using APV administered at CVRL in Soba, Khartoum (Abusalab *et al*., 2003). To create a bivalent vaccination, *P. multocida* strains B:2 and E:2 were mass-cultivated in an IBT-Gottingen bioreactor.

***Control***

Effective control of a variety of HS diseases will be aided by hygienic planning, immunoprophylaxis, chemotherapy, and fundamental management practices, including feeding and maintenance (Benkirane and De Alwis, 2002). Animal travel restrictions, particularly for unvaccinated animals, should be rigorously enforced in endemic areas (Rashid *et al*., 2008). When animals are transported from endemic to nonendemic regions, strict quarantine regulations must be implemented (Shome *et al*., 2024). To reduce the occurrence and transmission of disease, it is recommended to dispose of carcasses properly and to adopt improved husbandry techniques (Chanda *et al*., 2024). A greater understanding of the epidemiology of HS, improved vaccine development, and the introduction of nationwide vaccination campaigns can lead to more successful control of the disease.

The implementation of preventive measures seems to be the only viable strategy for HS management. To eradicate disease in endemic areas, systematic vaccination and early administration of antibiotics, particularly in isolated instances, have proven crucial (Tabatabaei *et al*., 2007). Vaccination is a common method of immunoprophylaxis, and in tropical regions, many kinds of inactivated vaccines, with or without adjuvants, have been employed (Verma and Jaiswal, 1998). Long-term immunity is thought to be provided via reinforcement through recurrent natural infections. Veterinarians who identify or suspect HS should adhere to local or national illness reporting rules. State or federal authorities shall be informed as soon as this condition is suspected or diagnosed.

## Conclusion

HS is an infectious disease caused by the bacteria *P. multocida*. HS has significant economic implications, particularly in Asia and, to a lesser extent, Africa. Most clinical cases have been reported in buffalo and cattle. Buffalo typically exhibit more severe symptoms and a shorter duration of disease. Effective control of various HS diseases will be aided by hygienic planning, immunoprophylaxis, chemotherapy, and fundamental management practices, including feeding and maintenance.

## Acknowledgments

The authors would like to acknowledge the Kementerian Pendidikan, Kebudayaan, Riset, and Teknologi who funded this research.

***Conflict of interest***
The authors declare no conflict of interest.
***Funding***
The authors thank Universitas Airlangga for their managerial support.
***Author's contributions***
TDL, ARK, BWKW, and SW drafted the manuscript. NA, DAAK, IFM, and IBM revised and edited the manuscripts. KAF, RZA, EFL, TH, and RD participated in preparing and critical checking of the manuscript. IF, SU, SM, RR, and MKJK edited the references. All authors read and approved the final manuscript.
***Data availability***
All references are open-access, so data can be obtained from the online web.

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