Review

Hemorrhagic Septicemia in Livestock: Molecular Insights, Epidemiological Dynamics, and Next-Generation Control Strategies

Running title: Next-Generation Approaches to Hemorrhagic Septicemia Management

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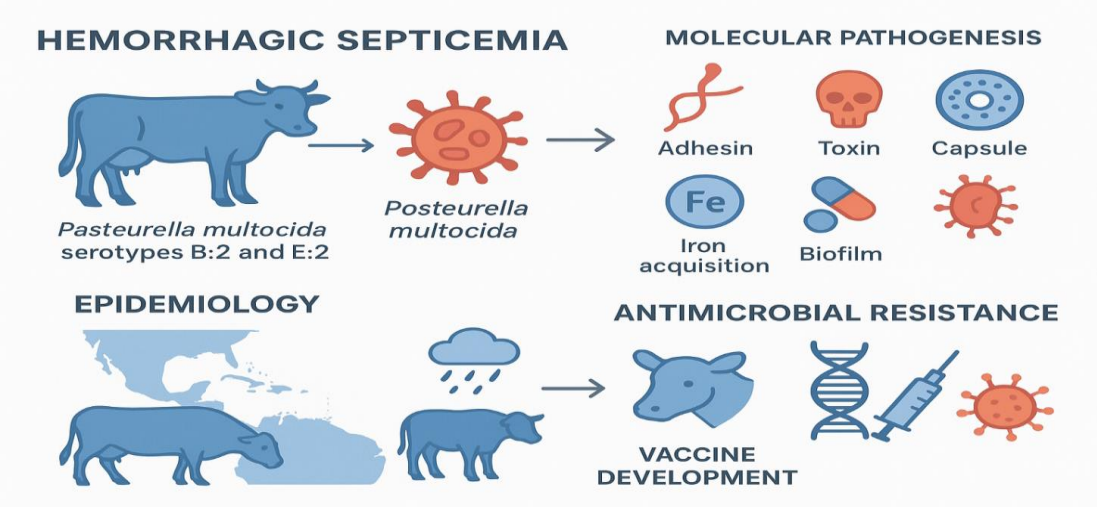
Abstract

Hemorrhagic septicemia (HS), caused by *Pasteurella multocida* serotypes B:2 and E:2, remains one of the most destructive bacterial diseases of cattle and buffalo in tropical and subtropical regions. Its hyperacute course, high mortality, and recurring outbreaks impose major economic losses, particularly on smallholder farming systems where food security and livelihoods are already fragile. Despite centuries of recognition, HS persists as a neglected threat due to complex molecular pathogenesis, dynamic epidemiology, and the rapid rise of antimicrobial resistance (AMR). At the molecular level, *P. multocida* deploys adhesins, toxins, capsules, iron acquisition systems, and biofilm formation to evade host immunity and trigger systemic septicemia. Comparative genomics underscores substantial strain diversity, plasmid-mediated resistance genes, and virulence islands, complicating therapeutic and vaccine development. Epidemiologically, HS is driven by geography, seasonal monsoon patterns, host susceptibility, and environmental reservoirs that maintain persistent transmission cycles. Conventional bacterin vaccines and antimicrobials, though historically central to control, often fail under field conditions, with resistance to sulfonamides, tetracyclines, macrolides, and β-lactams increasingly reported. Emerging strategies, including recombinant and DNA vaccines, live-attenuated and aerosolized platforms, and immunomodulatory approaches, show promise but remain insufficiently validated in endemic contexts. Parallel advances in multi-omics, precision livestock farming, and molecular surveillance provide new opportunities, yet face barriers of infrastructure, cost, and regulatory inertia. This review consolidates current insights into HS pathogenesis, epidemiology, antimicrobial resistance, and vaccine development, while identifying critical gaps and research priorities. Its scope is to bridge molecular discoveries with field-level applications, offering a framework for sustainable HS control and mitigation of its global burden.

Graphical Abstract



Keywords

Antimicrobial resistance; Hemorrhagic septicemia; Molecular pathogenesis; Multi-omics surveillance; *Pasteurella multocida* B:2 and E:2; Vaccine breakthroughs

1. Context

1.1 Introduction

Hemorrhagic septicemia (HS) is one of the most challenging problems in veterinary medicine, a hyperacute to acute septicemic illness that primarily affects cattle and water buffalo in tropical and subtropical regions of the world (1-3). For populations that depend on livestock, the disease's high fatality rates and quick onset have significant economic ramifications, especially in underdeveloped countries where animal husbandry is the mainstay of rural economies. The causative agent behind this destructive ailment is *Pasteurella multocida*; its serotypes B:2 and E:2 exhibit exceptional pathogenic potential. Figure 1. shows Circular representation of the *P.multocida* genome showing annotated virulence, antimicrobial resistance (AMR), core, and ribosomal RNA (rRNA) genes. Virulence genes (red) include ptx**,** ompH**,** pfhA**,** toxA**,** and tlyA, which are implicated in adhesion, immune evasion, and toxin production(4, 5). AMR determinants (orange) include blaTEM (β-lactam resistance), sul2 (sulfonamide resistance), and tetB (tetracycline resistance), consistent with recent surveillance reports of multidrug-resistant *P. multocida* (6, 7). Core housekeeping genes (green) such as recA, rpoB, and gyrB are essential for DNA repair, transcription, and replication. The rRNA operon (blue) contains the 16S-23S-5S rRNA genes, which are widely used for phylogenetic identification and strain typing. The smaller circle represents a plasmid harboring blaTEM and mobA, indicating the potential for horizontal gene transfer of resistance traits. Gene annotations were assigned using the Virulence Factor Database (VFDB) and ResFinder, and plasmid elements were identified with PlasmidFinder.

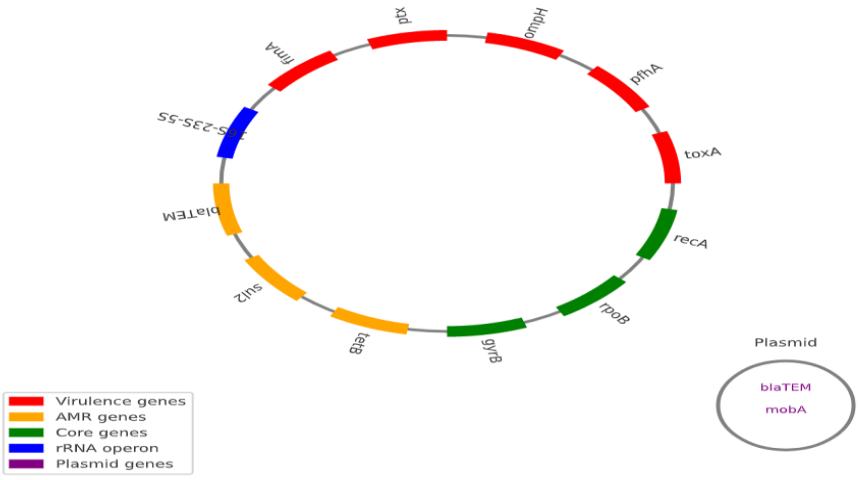


Figure 1. shows Circular representation of the *P.multocida* genome

Figure 2. shows Circular genome map of the *P.multocida* B2 strain.
On the chromosomal circle:

- Virulence genes (red): *plpE*, *ptx*, *ompH*, *toxA*, *hlyA*, associated with adhesins, toxins, and hemolysins(4, 8).
- Antimicrobial resistance genes (orange): *blaTEM* (β-lactamase), *sul2*, and *tetB*, conferring resistance to β-lactams, sulfonamides, and tetracyclines(7, 9).
- Capsule/iron acquisition genes (green): *bcbA*, *bcbB* (capsule biosynthesis) and *hgbA* (hemoglobin receptor)(10).

- rRNA operon (blue): 16S–23S–5S ribosomal RNA cluster(11).

The small circle depicts a self-replicating plasmid encoding *blaTEM* and *repA*, indicating potential for dissemination of resistance traits.

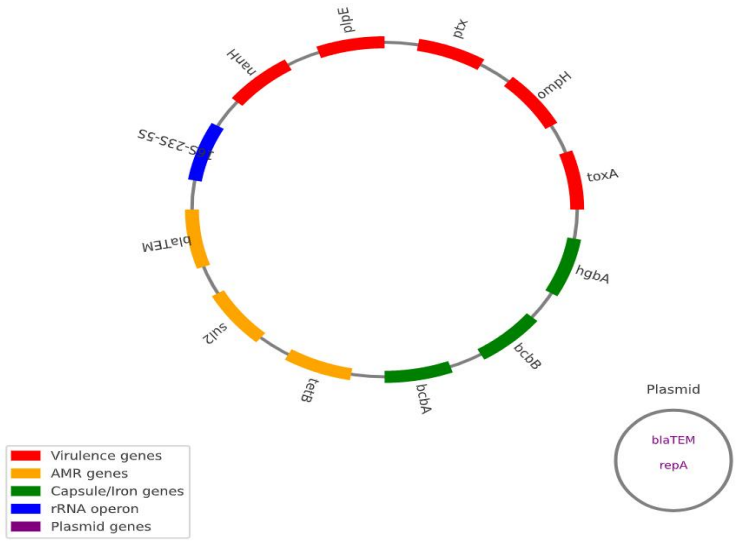


Figure 2. shows Circyar genome map of the *P.multocida* B2 strain

Figure 3. shows Genome map of *P.multocida* E:2 highlighting key virulence and resistance features.

Virulence genes (red) include *nanB* (neuraminidase), *plpE* (lipoprotein antigen), *ompH* (outer membrane porin), and *toxA* (dermonecrotic toxin), linked to adhesion, immune evasion, and host tissue damage(4).

Capsule/iron genes (green) include *hgbB* (hemoglobin receptor) and *ecbA/B* (serogroup E capsule biosynthesis)(6).

AMR genes (orange) *blaTEM*, *sul2*, and *tetB* confer β-lactam, sulfonamide, and tetracycline resistance(7, 9).

The rRNA operon (blue) contains the complete 16S–23S–5S cluster(10).

The plasmid (purple) carries *blaTEM* and *repA*, enabling resistance transfer. This genetic profile underpins the strain's high pathogenicity in hemorrhagic septicemia.

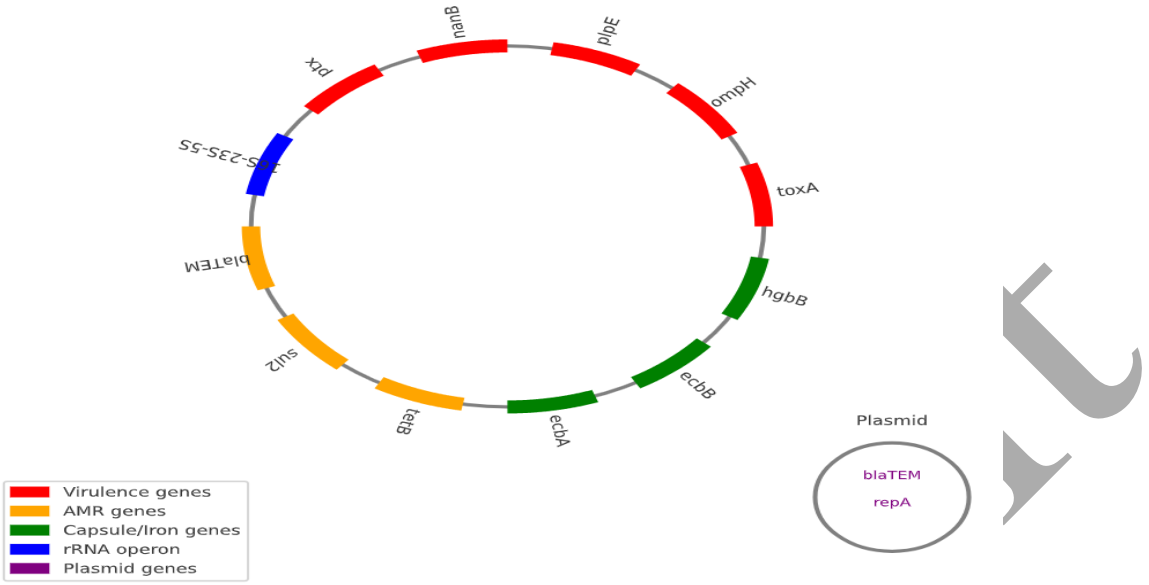


Figure 3. shows Circular genome map of the *P.multocida* E2 strain

P. multocida strains are classified into five capsular types (A, B, D, E, and F) based on the indirect haemagglutination test, 16 somatic serogroups based on the agar gel precipitation test, and eight LPS genotypes (L1–L8)(5). Within hours of infection, they can overpower the host's immune system and develop to systemic septicemia, which can have disastrous outcomes.

It is impossible to overestimate the historical significance of HS, as outbreaks have been reported for centuries. Nevertheless, the disease is still evolving and adapting, posing new difficulties for researchers and veterinary professionals(12, 13). A dynamic disease landscape needs ongoing monitoring and flexible management techniques due to the intricate interactions between environmental factors, host susceptibility, and pathogen virulence. Our capacity to examine the basic mechanisms of HS pathogenesis has been revolutionized by recent technology developments, which have revealed complex molecular systems that control host immune responses, bacterial virulence, and disease progression(1, 14).

Beyond the acute losses of cattle, HS has a substantial negative economic impact on food security in impacted areas due to decreased productivity, harmed breeding programs, and higher veterinary expenses. Smallholder farmers are disproportionately impacted by HS-related losses, which conservative estimates amount to hundreds of millions of dollars annually worldwide, because they have limited access to veterinary care and preventive measures. This economic reality emphasizes the need for effective, affordable, and long-lasting management techniques that function in a range of agricultural systems and socioeconomic contexts.

Current HS research has changed as a result of the application of state-of-the-art molecular techniques, high-throughput sequencing technologies, and systems biology methodologies. The discovery of new virulence factors, thorough examination of host-pathogen interactions at unprecedented resolution, and deep characterization of pathogen genetics have all been made possible by these methodological advancements. At the same time, epidemiological studies using

contemporary monitoring tools and analytical techniques have improved our knowledge of the dynamics of disease transmission, the identification of risk factors, and the capacity to anticipate outbreaks.

Microbiology, immunology, epidemiology, and veterinary medicine are among the scientific fields that must be integrated in order to establish effective prevention methods for HS(15, 16). Innovative preventative strategies must be investigated because traditional techniques that mainly rely on antimicrobial therapy and conventional vaccinations have demonstrated little success in various circumstances. Probiotics and prebiotics, immunomodulatory treatments, next-generation vaccination platforms, antimicrobial substitutes, and precision medicine techniques catered to particular host populations and epidemiological settings are examples of emerging tactics.
This review aims to critically synthesize current knowledge on HS, with emphasis on the molecular determinants of *P.multocida* virulence, epidemiological drivers of disease spread, antimicrobial resistance trends, and the performance of existing and emerging vaccines. The scope is to integrate molecular, epidemiological, and immunological perspectives, expose unresolved gaps in prevention and control, and highlight innovative approaches such as multi-omics tools, recombinant vaccine platforms, and advanced diagnostic strategies that could inform future research and field applications.

1.2 Molecular Pathogenesis

Hemorrhagic septicemia's molecular pathogenesis involves a complicated series of host immune reactions and bacterial virulence mechanisms that lead to systemic septicemia and frequently deadly consequences. The advanced molecular machinery of *P.multocida* serotypes B:2 and E:2 allows for quick colonization, immunological evasion, and systemic spread in vulnerable hosts(17, 18). Comprehending these molecular processes is essential for creating focused treatment plans and successful preventative measures.

Several adhesion factors, such as fimbriae, outer membrane proteins, and surface-associated polysaccharides, aid in the bacterial attachment and colonization of the upper respiratory tract during the early phases of HS pathogenesis. By mediating specialized interactions with host cell receptors and offering defense against early immune responses, the capsular polysaccharide, especially in serotype B:2 strains, plays a crucial role in initial colonizatio. According to recent molecular research, a number of adhesin proteins, such as PfhB1, PfhB2, and several autotransporter proteins, aid in bacterial attachment and the early onset of infection.

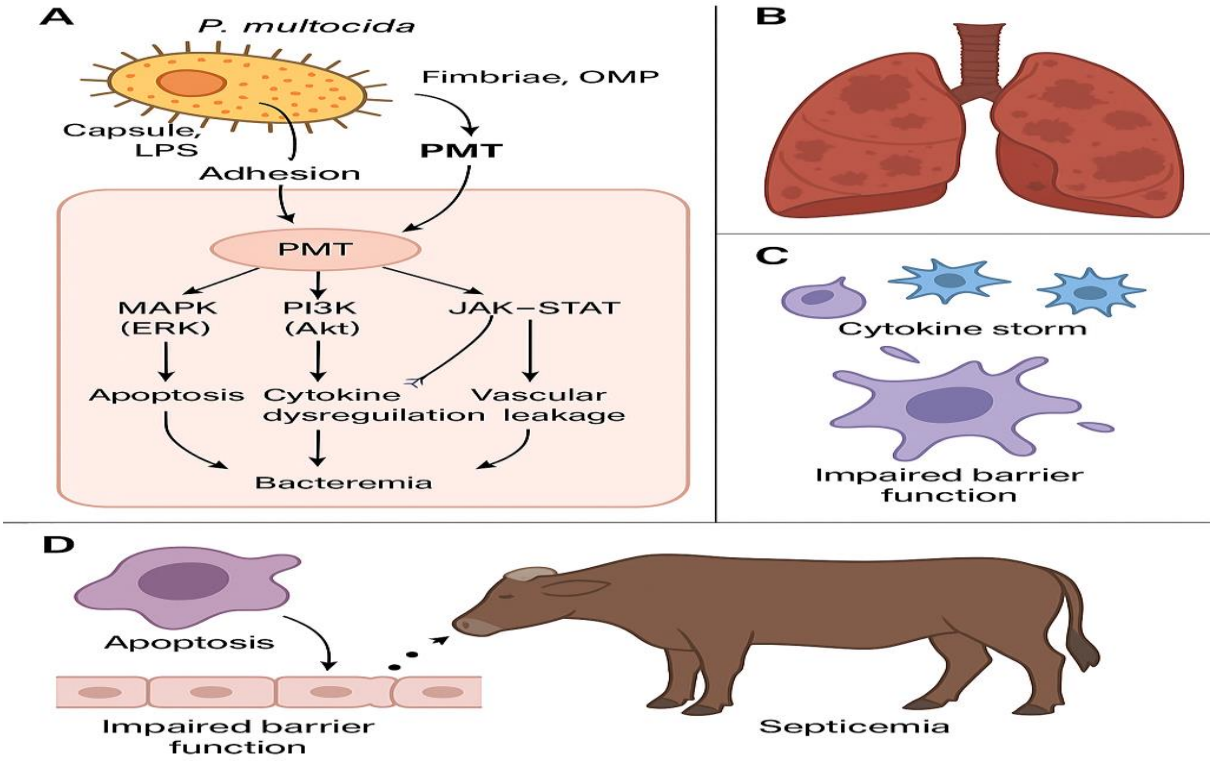


Figure 4. shows Molecular pathogenesis of hemorrhagic septicemia by *P.multocida*: Respiratory entry, immune evasion, endotoxin release, septicemia, vascular damage, and organ failure.

P. multocida uses a variety of virulence tactics to get past the host's immune system and cause a systemic infection after colonization is achieved. A key virulence mechanism is the generation of strong exotoxins, with cytolethal distending toxin (CDT) and dermonecrotic toxin (DNT) having particularly significant roles in pathogenesis(19, 20). The strong vasoconstrictive and inflammatory effects of DNT, which is encoded by the *toxA* gene, help explain the typical vascular damage and hemorrhagic lesions seen in HS patients (Figure 4). The toxin causes smooth muscle contraction, endothelial dysfunction, and increased vascular permeability by activating particular signaling pathways, such as the Rho/ROCK pathway.

P. multocida's capsular polysaccharide is an essential part of pathogenesis and vaccine development because it has two roles: it is a protective antigen and a virulence factor. Complex genetic mechanisms involving numerous gene clusters regulate the manufacture of capsular polysaccharides; recent genomic studies have shown that the arrangement of capsular genes varies significantly amongst serotypes(21, 22). The formulation of vaccines and cross-protective immunity are significantly impacted by these molecular variations.

Another essential virulence mechanism used by *P. multocida* during systemic infection is iron acquisition systems(23, 24). The pathogen has a variety of iron uptake routes, such as direct iron transport, heme consumption pathways, and siderophore-mediated acquisition. Recent transcriptome investigations have shown intricate regulatory networks controlling iron homeostasis during infection, demonstrating how host environmental factors and iron availability tightly regulate the expression of these systems. Bacterial survival and reproduction during systemic infection depend on their capacity to effectively compete for iron in the host environment that is iron-limited(25, 26).

Both innate and adaptive immunological mechanisms are involved in the host's immune response to *P. multocida* infection; nevertheless, the quick development of HS frequently overwhelms these

defenses(27, 28). Pattern recognition receptors (PRRs) are responsible for innate immune recognition by identifying pathogen-associated molecular patterns (PAMPs) on bacterial surfaces. Toll-like receptors (TLRs), especially TLR4 and TLR2, are crucial for the first immune recognition that triggers the generation of cytokines and inflammatory signaling pathways(29, 30). Nevertheless, *P. multocida* has developed a number of defenses against these immunological reactions, such as altering the structure of lipopolysaccharides and producing immune-suppressive substances(31, 32).

Massive cytokine production, including pro-inflammatory mediators like tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), is part of the inflammatory response triggered by *P. multocida* infection. Even though these reactions are initially protective, the excessive inflammatory cascade may be a factor in the pathological alterations that are typical of HS, such as aberrant coagulation, increased vascular permeability, and endothelial dysfunction. Certain inflammatory pathways have been identified by recent research as potential therapeutic targets for reducing overactive immune responses during HS.

Significant genetic variation has been found in the genomes of *P. multocida* strains linked to HS, and many putative virulence genes that aid in pathogenesis have been found. Comparative genomic research has revealed the presence of horizontally acquired virulence factors, mobile genetic elements, and pathogenicity islands that enhance the pathogenic potential of bacteria. Developing comprehensive preventive strategies that account for the genetic variability within the pathogen population and comprehending strain-specific virulence features are greatly influenced by these findings.

More attention has been paid to the role of biofilm formation in P. multocida pathogenicity since recent studies have demonstrated that HS-associated strains can form biofilms under specific environmental circumstances. In addition to increasing their resistance to antibiotics and preventing host immunological responses, the formation of biofilms may aid bacteria in surviving in environmental reservoirs. New therapeutic strategies that target these bacterial populations may be developed with an understanding of the molecular principles behind biofilm formation and dissemination.

The relationship between *P. multocida* and the host complement system is a key battleground in the pathophysiology of HS. The complement system is one significant innate immune defense mechanism that can both directly eliminate pathogens and aid in their removal by phagocytic cell. However, sophisticated complement evasion strategies, such as complement inhibitor production, surface antigen modification, and complement regulatory protein expression, have been established by successful *P. multocida* strains. Recent molecular research has revealed certain complement evasion pathways that may be targeted for therapeutic intervention.

1.3 Epidemiology and Risk Factors

The dynamics of sickness occurrence and transmission are influenced by the epidemiological landscape of HS, which is defined by various geographic distributions, seasonal patterns, and host vulnerability characteristics. Developing efficient monitoring systems, risk assessment procedures, and focused preventive initiatives requires an understanding of these epidemiological characteristics. Geographic information systems (GIS), powerful statistical modeling techniques, and improved molecular typing procedures have greatly aided modern

epidemiological investigations by offering deeper insights into disease patterns and transmission pathways.

HS exhibits a clear regional distribution, with the largest incidence rates found in tropical and subtropical regions of Asia, Africa, and the Middle East. India, Pakistan, Bangladesh, Myanmar, Thailand, Vietnam, Egypt, Sudan, and numerous other countries with sizable populations of cattle and water buffalo are among those where the disease is endemic.

There is ample evidence of seasonal fluctuations in the incidence of HS, with the majority of outbreaks taking place during monsoon seasons and times of high temperature and humidity. Because of a number of environmental factors, such as stress from weather changes, increased pathogen survival in humid conditions, and enhanced transmission through contaminated water sources and feed materials, the onset of monsoon rains usually corresponds with an increase in disease incidence. Changes in temperature, especially abrupt reductions in the surrounding air temperature, have been found to be important risk factors that put animals at risk for HS by weakening their immune systems and making them more vulnerable to infection.

Significant differences are seen between various animal species, breeds, age groups, and physiological conditions, and host variables are important in determining susceptibility to hemorrhagic septicemia. Although both animals can experience severe sickness, water buffalo often show a higher susceptibility to HS than cattle. Young animals are more susceptible to HS, especially those between the ages of six months and two years. This is probably because their immune systems are still developing, and their exposure-induced immunity is still limited. Due to immunological suppression and physiological stress related to reproductive processes, pregnant and nursing animals also exhibit increased susceptibility.

There is evidence of breed-specific susceptibility patterns, with native breeds frequently exhibiting higher levels of HS resistance than exotic or crossbred animals.

HS susceptibility is strongly influenced by nutritional state; animals that are malnourished exhibit higher susceptibility to infection and more severe illness consequences. Protein, energy, vitamin, and trace mineral deficiencies in particular impair immunological function and lessen the animal's capacity to build a successful defense against *P. multocida* infection. By producing times of heightened host sensitivity, seasonal fluctuations in feed quality and availability, which are typical in many endemic regions, contribute to temporal patterns of HS incidence.

Management and husbandry techniques are important risk factors for the development and spread of hemorrhagic septicemia. The danger of disease is raised by overcrowding, inadequate ventilation, poor sanitation, and the mixing of animals from various sources. Sharing water supplies and engaging in communal grazing encourage the spread of pathogens among animals and herds. A major contributing factor to HS epidemics is transportation stress, namely, related to the long-distance movement of animals for commerce or seasonal migration.

Beyond climate, environmental factors such as vegetation patterns, soil properties, and water quality are significant in HS epidemiology. Under ideal circumstances, the virus can persist in the environment for long stretches of time, and polluted water sources, feed sources, and facilities are significant infection reservoirs. *P.multocida* has been found in a variety of environmental samples by recent environmental monitoring investigations, underscoring the significance of environmental contamination in disease transmission cycles.

Numerous species, including birds, other mammals, and wild ruminants, have been identified as *P.multocida* wildlife reservoirs(33-36). In addition to potentially contributing to spillover infections in domestic livestock populations, these animal populations can act as maintenance hosts for the virus. Comprehensive disease control techniques require an understanding of *P.*

multocida ecology in wildlife populations, especially in regions where domestic animals and wildlife share resources or habitats. A schematic representation of the major epidemiological risk factors influencing HS occurrence is provided in Figure 5.

An increasingly significant epidemiological problem is the development of antibiotic resistance in *P. multocida* population. Selection pressure favoring resistant strains has resulted from the widespread use of antimicrobial medicines for both prevention and treatment. Resistance to several kinds of antimicrobials frequently used in the treatment of HS, such as tetracyclines, sulfonamides, and fluoroquinolones, has been reported in recent surveillance investigations(37-40). The emergence of this resistance has significant ramifications for the effectiveness of therapy and underscores the importance of using antibiotics sparingly and employing alternative management methods.

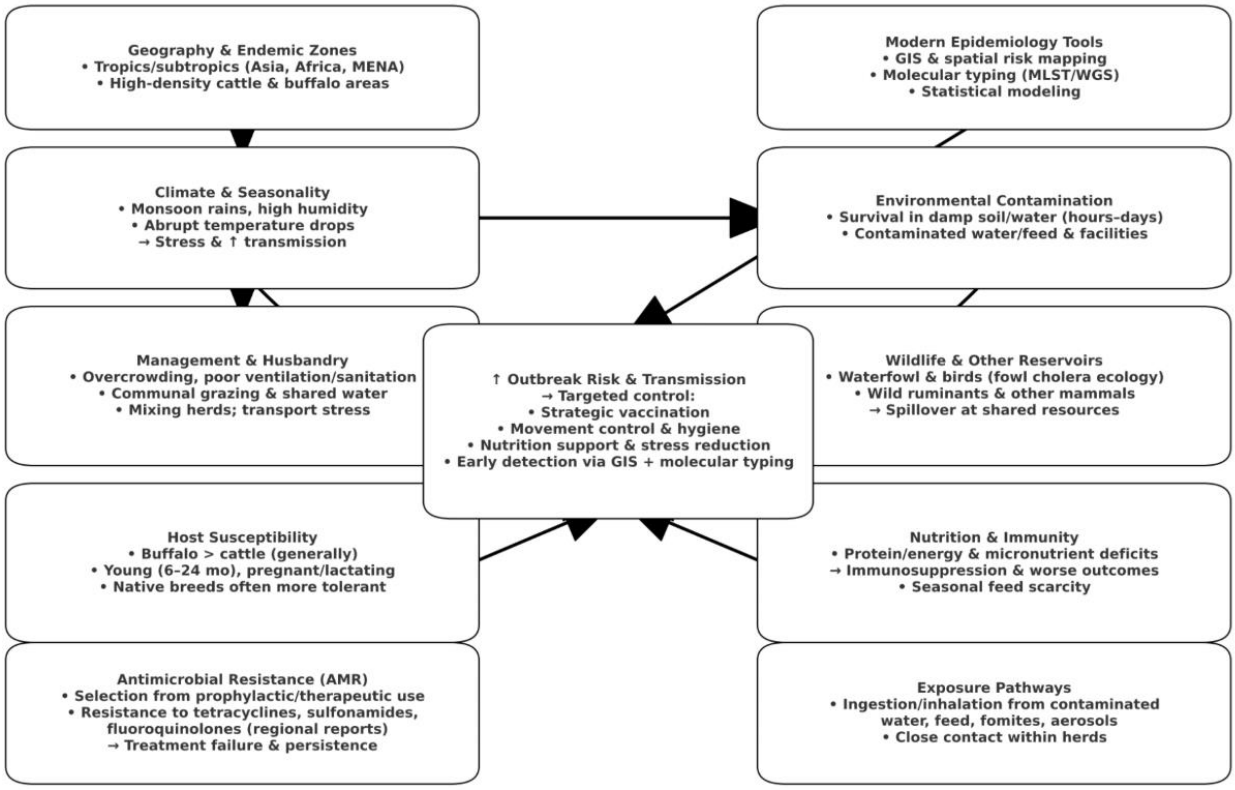


Figure 5 shows a Flowchart illustrating the epidemiological determinants and risk factors driving HS outbreaks, as well as potential control strategies.

2. Data Acquisition

The data for this review were collected from peer-reviewed scientific databases including PubMed, Scopus, and Web of Science. Keywords such as "hemorrhagic septicemia," "*Pasteurella multocida*," "virulence factors," "epidemiology," "antimicrobial resistance," and "vaccine development" were used in various combinations. Articles published between 2000 and 2025 were prioritized, with emphasis on studies employing molecular, genomic, and epidemiological methodologies. Reference lists of key papers were screened to identify additional relevant sources. Reports from the World Organisation for Animal Health (WOAH/OIE) and regional surveillance

bulletins were also incorporated to ensure comprehensive coverage of both global and endemic perspectives.

3. Results

3.1 Current Prevention and Control Strategies

Contemporary prevention and control of HS operates at the strained intersection between antiquated bacterin regimens, evolving *P.multocida* biology, and emergent biotechnological aspirations. Conventional strategies remain heterologous and reactive vaccination with whole-cell, oil-adjuvanted bacterins persists as the backbone of prophylaxis in endemic zones, despite demonstrable inconsistencies in efficacy (often dwindling below 60 percent field effectiveness) and frequently waning immunogenicity within 6–12 months post-administration. However, the molecular underpinnings behind this variable efficacy, whether poor epitope conservation, formulation instability, or cold-chain breaches, remain poorly elucidated (41, 42).

Recent advances have introduced refined vaccine prototypes, notably recombinant PmSLP3-based formulations active against both B and E serogroups, which show extended immunogenicity and superior cross-protection in bovines. Yet, the absence of large-scale field validation, dose-sparring studies, and correlate of protection assays severely limits their translatability. Technological surveillance reveals a cautious upsurge in novel vaccine platforms globally, yet effective commercial deployment remains thwarted by regulatory inertia and cost-effectiveness uncertainty. In parallel, antimicrobial therapy continues to be employed both therapeutically and prophylactically. A recent Pakistan-based molecular epidemiology investigation exposed an alarming prevalence of resistance: trimethoprim/sulfamethoxazole (≈70 %), erythromycin (≈68 %), and a worrying emergence of β-lactamase genes including bla_TEM, bla ROB-1, bla OXA-2, and NDM (New Delhi Metallo-β-lactamase) variants in *P. multocida* isolates(43). Surveillance in Hungarian waterfowl, while somewhat reassuring in continued general antimicrobial susceptibility, noted resistance creeping into enrofloxacin usage, suggesting a creeping resistance drift. Still, systematic AMR surveillance across endemic and especially wildlife reservoirs remains scant, creating a blind spot in stewardship and therapeutic guidelines.

Management interventions, structural biosecurity reforms, movement restrictions, nutritional optimization, housing ventilation, and all-in/all-out systems are undeniably low-tech pillars of HS control. Yet, rigorous evaluation of their measurable impact on HS incidence, seasonality modulation, or economic cost-benefit remains frustratingly rare. Moreover, the epidemiological role of wildlife (e.g., wild ungulates, antelope, cervids) as cryptic reservoirs capable of sustaining and transmitting HS remains speculative; interspecies transmission pathways are poorly mapped except for anecdotal serotype detection reports. Similarly, predictive molecular surveillance, real-time genotyping, serotype drift mapping, and virulence island monitoring are almost non-existent in many endemic regions, leaving emergent lineage shifts dangerously invisible until outbreak emergence. In sum, while the architecture of HS prevention integrates vaccines, antimicrobials, husbandry, biosecurity, and surveillance, each pillar is undermined by gaps in validation, execution fidelity, and ecological realism. That fragmentary mosaic renders HS an archetypal

neglected disease common in scale and impact, yet insufficiently interrogated at the molecular epidemiological nexus to contain its re-emergence reliably.

3.2 Emerging Prevention Strategies

The trajectory of HS prevention is pivoting from conventional tactics to a constellation of avant-garde biotechnologies, systems-immunology designs, and precision livestock medicine paradigms. These emerging modalities, while still embryonic, reflect a shift toward highly safe, targeted, and context-adaptable interventions. The molecular toolkit spans rational antigen selection, gene-delivery platforms, nanoscale engineering, and host-centric immuno-modulation.

3.2.1 Recombinant vaccine platforms now transcend whole-cell bacterins, targeting discreet *P. multocida* antigens such as conserved outer-membrane proteins (e.g., OmpH) and transferrin-binding components offering antigenic specificity, reproducibility, and streamlined production. Experimental data on recombinant OmpH from *P. multocida* B:2 strains tested in murine models and rat challenge systems demonstrated robust IgG responses and partial to near-full protection, substantially outpacing killed vaccine benchmarks(44).

3.2.2 DNA vaccines, engineered to encode OmpH or transferrin-binding protein A (TbpA), herald a promising frontier. Constructs delivered via mammalian expression vectors (e.g., pUCP24-OmpH or bicistronic TbpA IL2) induced potent humoral and cellular immunity in rodents, with enhanced antibody titers and measurable lymphocyte proliferation even without adjuvants, suggesting durable genetic immunogenicity(44, 45). Notably, TbpA constructs fused to IL-2 augmented immunostimulation, hinting at a route for molecular adjuvant integration.

3.2.3 Live attenuated and aerosol vaccine vectors like aroA-deficient *P. multocida* B:2 strains and non-pathogenic aerosolized formulations are re-emerging as viable strategies. Intramuscular administration of an aroA mutant conferred solid protection in calves, whereas intranasal delivery proved inconsistent, underscoring route-dependent efficacy. A live aerosol vaccine trial in buffalo and cattle reported significantly elevated antibody titers and complete challenge protection, with the added benefit of reducing vaccination frequency in field-applicable settings(46).

3.2.4 Nanoparticle and vectored systems, mucosal administration, immunomodulators, and precision medicine remain largely aspirational. No robust data exist yet for nanoparticle-facilitated HS vaccines, viral-vectored platforms (e.g., adenovirus, NDV), or mucosal delivery systems specifically tailored for HS, despite their theoretical promise. Likewise, interventions such as cytokine adjuvants, probiotic-based modulation, phage therapy, or antimicrobial peptides are conspicuously absent in HS-specific literature reflecting a yawning translational gap(13, 47).

3.2.5 Precision prevention frameworks, although strain-typing using MLST, PFGE, and whole-genome sequencing has enhanced our understanding of HS epidemiology (e.g., dominance of ST122 across Pakistan and Thailand; genomic divergence between circulating field strains and vaccine strain P52), no peer-reviewed study has leveraged this data to guide

precision prevention, such as host-genotype-informed breeding or pathogen strain-matched vaccination. Thus, precision frameworks remain purely theoretical(48).

3.3 Future Directions and Research Priorities

The trajectory of hemorrhagic septicemia (HS) research must increasingly align biotechnological sophistication with pragmatic, field-level realities, as conventional diagnostic and prophylactic strategies remain insufficient to curb recurrent outbreaks in endemic regions. Several interdependent domains illustrate both the opportunities and glaring lacunae in the current knowledge landscape:

3.3.1 Multi-Omics and Systems Biology Integration

Despite rapid advances in host-pathogen interaction studies, true multi-omics integration (genomics, transcriptomics, proteomics, metabolomics) in HS remains embryonic(49). The absence of standardized pipelines, open-access omics repositories, and curated reference genomes of virulent *P. multocida* B:2 and E:2 strains hampers systems-level inference of virulence dynamics and host immune evasion. Cross-species comparative frameworks, widely used in human and zoonotic pathogens, remain underdeveloped for HS.

3.3.2 Artificial Intelligence and Predictive Epidemiology

AI-enabled modeling offers theoretical promise for outbreak prediction and antimicrobial stewardship. However, algorithms remain hamstrung by data sparsity, geographical bias, and minimal real-world validation in low- and middle-income countries (LMICs)(50). Integration of meteorological and livestock mobility datasets into machine-learning pipelines is particularly underexplored.

3.3.3 Precision Livestock Farming (PLF) Technologies

Wearable sensors, automated thermal imaging, and biosignal monitoring are reshaping livestock surveillance in high-income contexts, but their translational potential for buffalo and cattle in HS-endemic rural Asia and Africa is largely aspirational(51). The prohibitive costs, infrastructural constraints, and absence of local technical support impede their practical deployment at scale.

3.3.4 Rational Vaccine Design and Next-Gen Platforms

Recombinant outer-membrane lipoproteins (e.g., PmSLP-3) have demonstrated broad serogroup protection and extended immunogenicity in bovine models under experimental conditions(52). Similarly, OmpH-DNA vaccine constructs outperform conventional bacterins in rodents, yet bovine challenge studies remain conspicuously absent. Stability under field conditions, cold-chain independence, and cross-protection trials remain critical bottlenecks.

3.3.5 Aerosolized and Route-Dependent Vaccination

Recent buffalo trials suggest attenuated *P. multocida* B:2 aerosol vaccines elicit superior mucosal immunity and long-lasting protection compared to oil-adjuvanted bacterins(53).

However, ecological safety, horizontal transmission risk, and thermostability in field deployment have not been systematically investigated.

3.3.6 Antimicrobial Resistance (AMR) Monitoring and Alternatives

Global antimicrobial resistance (AMR) surveillance increasingly flags *P.multocida* ,the culprit in HS as a rising livestock health threat across Asia and Africa. A recent study from Punjab, Pakistan, reported a 7.57% prevalence of *P. multocida* in HS-affected cattle and buffalo, with roughly 70% of isolates resistant to trimethoprim , sulfamethoxazole, and 67.5% to erythromycin; about 31.5% harbored β-lactamase genes, including blaTEM, blaROB-1, blaOXA-2, and blaNDM(54). These findings mirror regional and global patterns where overuse of antimicrobials in livestock fuels escalating resistance.

4. Conclusion

Hemorrhagic septicemia remains one of the most formidable bacterial diseases of livestock, disproportionately affecting regions where surveillance, vaccination, and therapeutic options are limited. Despite decades of research, *P.multocida* continues to challenge control strategies through its genetic diversity, complex virulence mechanisms, and emerging antimicrobial resistance. Current vaccines, although widely used, often provide incomplete protection, underscoring the urgent need for innovative immunization approaches tailored to field conditions. Advances in molecular epidemiology, genomics, and recombinant vaccine platforms offer promising avenues for overcoming these barriers, yet their translation into cost-effective, field-ready solutions remains slow. To effectively curb HS, future efforts should prioritize integrated molecular and epidemiological studies, standardized AMR monitoring, and the development of next-generation vaccines that confer broad and durable immunity. By bridging laboratory insights with field realities, researchers and policymakers can close critical knowledge gaps and establish sustainable strategies to protect livestock health and productivity. Such progress is not only essential for improving animal welfare and farmer livelihoods but also for ensuring the resilience of livestock-dependent economies in endemic regions.

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Author's Contribution:

Concept and design of the study: SR
Methodology and data interpretation: MMA
Literature review and compilation: SZ
Drafting of the manuscript: SR, MWG, SZ
Critical revision of the manuscript for important intellectual content: MWG
Editing and proofreading: SZ
Supervision and final approval of the version to be published: MWG

Ethical Standards:

The present work is a narrative review of previously published studies. It does not contain any new data involving human participants or animals conducted by the authors. All sources of information have been properly acknowledged.

Data Availability

This review is based on previously published studies, all of which are cited in the reference list. No new datasets were generated. Additional insights represent the authors' perspectives and interpretations of the existing literature. AI tools were used only to generate illustrative figures in alignment with the manuscript's original concepts; no AI assistance was used in writing, analysis, or interpretation of the text.

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