Review

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Posted Date: 4 December 2025

doi: 10.20944/preprints202512.0400.v1

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 doi:10.20944/preprints202512.0400.v1

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Bacterial Bovine Respiratory Disease: A Comprehensive Review of Etiology, Pathogenesis, and Management Strategies

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Abstract

Bovine Respiratory Disease (BRD) represents one of the largest causes of economic loss and animal morbidity in the global cattle industry, second only to neonatal diarrhea. Its etiology is complex, originating from a multifactorial combination of host susceptibility, environmental stressors, viral infections, and secondary bacterial pathogens. Although viruses are often the initial cause of disease, suppressing the host's respiratory defense mechanisms, most of the severe pneumonic damage and clinical signs can be attributed to bacterial infections. This review provides an overview of the primary bacterial agents identified within the BRD complex, including *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni*, and *Mycoplasma bovis*. We discuss their role as commensals that then become opportunistic pathogens, and further how they interact in a synergistic relationship with a primary viral insult, leading to the resulting pathogenesis and the development of pneumonia. This manuscript discusses in further detail some of the challenges in BRD management, such as the limitations of current diagnostic methodologies, overreliance on antimicrobial therapy, and the growing concern of antimicrobial resistance. Lastly, the need for integrated approaches in management, better husbandry and biosecurity, coupled with the development of novel therapeutic alternatives, is underlined as a means of assuring a sustainable control of this serious syndrome.

Keywords: Bovine Respiratory Disease (BRD); *Mannheimia haemolytica*; *Pasteurella multocida*; *Histophilus somni*; *Mycoplasma bovis*; AMR

1. Introduction

Bovine Respiratory Disease (BRD) is a polymicrobial syndrome encompassing a range of respiratory disorders affecting the lower respiratory tract of cattle. Following neonatal diarrhea, BRD is the most common disease in the cattle industry. Therefore, it is a prime cause of huge economic losses, especially in pre-weaned calves [1]. These losses occur due to direct treatment costs, reduced animal performance, and mortality, which impose a massive financial burden on producers [2,3]. The economic impact is still increased by the indirect costs, involving decreased carcass quality and longer times to market. It is estimated that the US beef industry alone loses over $4 billion annually [2,3].

BRD has a multifactorial etiology that involves a complex interaction between host susceptibility, environmental stressors, and a wide range of viral and bacterial pathogens [1]. Key environmental stressors comprise transportation, weaning, handling, and over-crowding, which can induce immunosuppression, hence increasing the susceptibility of the host animals [1]. The impact of this transport-related factor is so significant that this syndrome has earned another common synonym: “shipping fever.” These stressors, along with poor ventilation and improper hygiene management, facilitate primary viral infection by several virus such as Bovine Respiratory Syncytial

 doi:10.20944/preprints202512.0400.v1

Virus (BRSV), Parainfluenza-3 Virus (PI-3V), Bovine Herpesvirus-1 (BoHV-1), and Bovine Viral Diarrhea Virus (BVDV) [4]. These viruses compromise the respiratory mucosa, thus creating a conducive environment for secondary bacterial colonization and proliferation [3–6].

These secondary bacterial infections are, however, the primary cause of the severe clinical signs and pulmonary damage that characterize BRD, even though the diseases are often initiated by viral infections [7]. The most common bacterial pathogens belong to the *Pasteurellaceae* and *Mycoplasmataceae* families. Specifically, *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni* are commensals of the upper respiratory tract of healthy cattle but can become opportunistic pathogens and descend into the lower respiratory tract following viral injury [8,9]. Their virulence factors, including lipopolysaccharides and cytotoxins, are crucial for overcoming host defenses and establishing infection [2]. In a similar way, *Mycoplasma bovis* is a widespread agent of high morbidity. The interrelation between viruses and bacteria leads to inflammation, lesions in lung tissue, and a reduction in the capacity for gas exchange, which clinically shows itself in a progressive development from nonspecific signs of disease such as inappetence and depression to frank respiratory signs that include nasal discharge, coughing, tachypnea, and dyspnea.

A significant challenge in BRD management is the difficulty of early and accurate diagnosis. The most common current practice involves visual-clinical assessment by barn staff, which is highly subjective and has low sensitivity, partly because cattle, as prey animals, instinctively mask signs of illness [10]. This usually results in late detection and treatment. Moreover, the non-specificity of clinical signs implies that a large proportion of treated animals might not have BRD, adding to the excessive use of antibiotics. This practice raises serious concerns regarding the selection and spread of antimicrobial resistance (AMR), a factor that represents a wider risk to public health via the food chain and environment. Increased diagnostic specificity, possibly through advanced imaging or biomarker analysis, becomes important for more prudent use of antimicrobials and better control [11,12]. To date, specific studies have been conducted on novel, advanced diagnostic techniques.

Given the central role of bacterial agents in the most severe stages of BRD and as the main targets of intervention, this work will focus on the main bacterial infectious agents involved. We will review their pathogenesis, the current and emerging therapeutic strategies, besides preventive measures that mitigate their noxious effect. The worsening of this complex syndrome, due to its economic and animal welfare impacts, requires a deeper understanding of these bacterial components and the development of new intervention strategies [13–15]. Therefore, particular emphasis will be placed on the growing crisis of antimicrobial resistance among these pathogens and the urgent need for innovative and integrated control programs, as well as new therapeutic strategies, to achieve sustainable mitigation of the economic and welfare burdens imposed by this disease.

2. Etiology of Bacterial Bovine Respiratory Disease

2.1. Pasteurella multocida

P. multocida is a Gram-negative bacterium that can infect a wide range of domestic mammals and birds. It was first discovered by Louis Pasteur around 1881 during investigations into the etiology of fowl cholera [16,17]. It is currently classified into five capsular groups and 16 somatic serotypes. In cattle, *P. multocida* A:3 is the serotype most isolated from animals with BRD, and its pathogenicity has been confirmed by experimental studies [18]. Furthermore, serogroups B, E, and F can be pathogenic in this species [19]. *P. multocida* infection in cattle can cause various types of bronchopneumonia, ranging from subacute to chronic fibrinopurulent, as well as fibrinous and fibro-necrotic forms. These may be accompanied by varying degrees of intra-alveolar hemorrhages and moderate to severe infiltration of neutrophils and macrophages in the bronchi and bronchioles [20]. Vaccines to prevent *P. multocida* infection include bacterins, which are used alone or, more commonly, in combination with other viral etiological agents [21]. The primary available treatments are antibiotics, such as amoxicillin, tilmicosin, and florfenicol, although growing antibiotic resistance has been recently reported [22]. Some National Institutes can also prepare autogenous vaccines. This process involves

 doi:10.20944/preprints202512.0400.v1

isolating *P. multocida* from organs with lesions or from nasal swabs taken from sick cattle, following careful nostril disinfection. The vaccine consists of a formalin-inactivated broth culture adjuvanted with aluminum hydroxide. It is administered subcutaneously at 5 ml/head, with a booster dose repeated after 20 days. Some modified live vaccines administered intranasally show good efficacy. This method allows for earlier vaccination without interfering with maternal immunity, leading to a strong local immune response and significant interferon production. Despite these efforts, the efficacy of bacterial vaccines against BRD pathogens, particularly in feedlot settings, remains a subject of debate due to inconsistent and limited results [2].

2.2. Mannheimia haemolytica

M. haemolytica is another significant Gram-negative bacterium contributing to calf pneumonia. Previously known as *Pasteurella haemolytica*, a revision of the *Pasteurellaceae* family classification, based on genomic homology, led to its reclassification into a new genus, *Mannheimia* [23]. Currently, *M. haemolytica* is categorized into 12 capsular serotypes. Serotypes A1 and A6 are predominantly associated with respiratory disease in cattle [24]. *M. haemolytica* possesses several virulence factors, including adhesins, fimbriae, capsular polysaccharides, and neuraminidase, which facilitate adhesion to the respiratory mucosa. Other factors include immunomodulatory and protective elements, as well as pro-inflammatory agents like lipopolysaccharide A endotoxin [25]. Infected animals may initially exhibit general clinical signs, such as fever, loss of appetite, and weight, alongside respiratory signs like cough, nasal discharge, and respiratory distress. Acute fibrinous pleuropneumonia, resulting from the obstruction of bronchioles and alveoli with fibrinous exudate, is the main cause of death [26]. Necropsy commonly reveals fibrinous pneumonia, a necrotizing inflammatory response, and alveolar damage and necrosis, primarily due to the infiltration of neutrophils and macrophages into the lung and fibrin deposition in the alveoli [24]. Therapy involves administering various antibiotics, such as florfenicol, ceftiofur, tilmicosin, tulathromycin, and quinolones, sometimes in conjunction with anti-inflammatories. Vaccines containing *M. haemolytica* leukotoxin, its primary virulence factor, are currently available [27]. However, scientific literature currently lacks sufficient data to confirm the full efficacy of this preventive measure [28]. A clinical study evaluated the intranasal administration of a *Lactobacillus* strain to prevent *M. haemolytica* colonization of the upper respiratory tract, suggesting a potential future avenue for bovine pneumonia prevention [29]. Furthermore, exploring novel vaccine formulations that target multiple virulence factors or incorporate adjuvants to enhance immune responses could improve protective efficacy against *M. haemolytica* [6].

2.3. Histophilus somni

H. somni is a Gram-negative bacterium that primarily affects cattle but can occasionally infect small ruminants [30]. Unlike *P. multocida* and *M. haemolytica*, circulating strains of *H. somni* are not currently classified into specific serotypes, and a complete nomenclature is not available to date. It was first isolated in, 1956 from cattle suffering from meningitidis [31]. While animals of all ages can be affected, recent findings suggest that weaned calves are at a higher risk of infection [32]. Although *H. somni* is considered, like other members of the *Pasteurellaceae* family, a commensal bacterium of the nasal tract, various strains have also been isolated from urogenital secretions, suggesting a potential role in venereal spread [33]. When the bacterium colonizes the lungs and accesses the bloodstream, it can cause a systemic disease extending beyond the respiratory tract. *H. somni* infection can also cause encephalitis, myocarditis, and sudden death from acute septicemia [34]. Post-mortem findings in the lungs include bronchopneumonia and fibrinous pleuritis [35]. Diagnosis based on macroscopic lesions is typically confirmed through culture isolation and molecular tests. Therapeutic options include broad-spectrum antibiotics, such as florfenicol. However, like *M. haemolytica*, while bacterins are currently available as a preventive measure, they have not demonstrated effective protection in vaccinated animals [36]. This highlights the need for continued research into more efficacious vaccines or alternative preventive strategies against *H. somni* [6].

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2.4. *Mycoplasma bovis*

M. bovis is a distinct bacterium, differing significantly from those previously described, and it presents one of the most significant challenges among BRD-associated pathogenic bacteria. First isolated in 1961[37], *M. bovis* is responsible for outbreaks of pneumonia in calves and young cattle, as well as mastitis in dairy cows, otitis, and occasionally abortion [38]. As with other members of the *Mycoplasmataceae* family, it is one of the smallest known bacteria and lacks a cell wall, rendering it naturally resistant to several classes of antibiotics [39]. *M. bovis* can exacerbate the severity of respiratory disease in calves, leading to increased morbidity and mortality rates [40]. Infected animals may exhibit clinical signs such as fever, depression, nasal discharge, shallow breathing, and coughing. Post-mortem examination often reveals bronchopneumonia characterized by caseous necrotic lesions, alongside fibrino-suppurative bronchopneumonia [41]. The pathogen also contributes to persistent inflammation and treatment failure in mixed infections. The absence of a cell wall also makes *M. bovis* intrinsically resistant to beta-lactam antibiotics, complicating treatment protocols and necessitating alternative antimicrobial strategies [3].

Preventing and controlling *M. bovis* largely relies on the careful introduction of new, healthy animals into herds. Pre-introduction ELISA testing to assess prior exposure, coupled with molecular detection for suspected individuals, offers an effective strategy to manage latent or new infections. Furthermore, effective management practices include adequate ventilation, thorough cleaning and disinfection of animal areas, careful control of milk-based feeding, regular monitoring of clinical signs, and prompt isolation of infected or treated animals. Once established in a herd, eradication proves challenging due to its robust environmental resistance and propensity for direct-contact transmission [42]. Its nature as a persistent intracellular bacterium, compounded by its lack of a cell wall, severely limits antibiotic treatment options, posing a significant barrier to eradication. Moreover, additional challenges stem from the high antigenic variability of its surface glycoproteins, which enable it to effectively evade the host's immune system [43]. The efficacy of treatment is often debated, as treated animals frequently relapse after a few weeks, partly attributed to increasing antibiotic resistance [44]. While several inactivated and live attenuated vaccines are commercially available, they primarily reduce lesion severity rather than providing complete protection against infection [43]. *M. bovis* can maintain viability for months in low-temperature environments and for weeks at room temperature on various substrates, further complicating its elimination from infected herds [45]. The fastidious nature of *M. bovis*, requiring specialized media and techniques for isolation, further hinders diagnostic efforts, contributing to its persistent presence in affected populations [2,46]. Rapid and accurate pen-side diagnostic tests or a combination of tests is therefore crucial for identifying and culling infected animals before the infection spreads throughout the herd, particularly when new animals are introduced or segregation is required [47].

2.4.1. Secondary Bacterial Pathogens

Secondary bacterial pathogens are also important. These organisms often capitalize on immunosuppression or prior viral insult to establish infections, contributing significantly to the complexity and severity of bovine respiratory disease [4]. They often colonize the respiratory tract after viral infections or environmental stressors, leading to severe pneumonia and pleuritis that are hallmarks of bovine respiratory disease complex.

The following pathogens play a crucial role in this second, bacterial phase.

Bibersteinia trehalose. The pathogen previously classified as *Pasteurella trehalosi* is phylogenetically and pathogenically very similar to *M. haemolytica*. It is a common commensal of the tonsils and nasopharynx that acts as an opportunistic pathogen, causing severe fibrino-necrotic pneumonia and septicemia. Its primary virulence factor is a leukotoxin (Lkt) that is immunologically cross-reactive with the leukotoxin of *M. haemolytica*. This toxin causes lysis of neutrophils and macrophages, leading to intense inflammation and damage to tissues. It is especially important in young, recently weaned or transported beef calves. There is some evidence that its prevalence is increasing in feedlots, possibly due to widespread vaccination against *M. haemolytica* [24,48].

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Trueperella pyogenes is a true secondary invader or tertiary pathogen. It is seldom a primary cause of acute pneumonia, but it is unusually adept at colonizing lungs whose integrity has been compromised by viruses or other bacteria. Its involvement often signals a transition to a chronic, suppurative pneumonia. It is a pyogenic bacterium, and it promotes the formation of pus and pulmonary abscesses. Infections complicated by *T. pyogenes* are often much more serious, chronic, and refractory to therapy because antibiotics cannot adequately penetrate the walled-off abscesses. Pyolysin, a pore-forming hemolysin, is its major virulence factor and is toxic to pulmonary epithelial cells and immune cells [49,50].

Pseudomonas aeruginosa rarely causes primary outbreaks in the field but is an important etiologic agent of nosocomial pneumonia. It is a major problem in calves that have been previously treated with antimicrobials or have received invasive procedures. *P. aeruginosa* is an environmental bacterium known for its intrinsic and acquired multidrug resistance. It also can form biofilms and survive in disinfectants, allowing it to contaminate veterinary equipment such as multidose vials, endotracheal tubes, and nebulizers. Many outbreaks have been traced back to a common contaminated source within the treatment facility [51,52].

Other pathogens like *Escherichia coli*, and *Streptococcus* spp. (including *S. dysgalactiae*, *S. uberis*) are generally considered opportunists that may be isolated from polymicrobial infections. They are more likely to be significant in neonates or severely immunocompromised animals [53].

Escherichia coli: While more famous for enteric disease, certain strains can cause septicemia and be isolated from pneumonic lungs, usually in very young, immunocompromised calves or as part of a polymicrobial infection.

Streptococcus spp.: Various *Streptococcus* species (e.g., *S. dysgalactiae*, *S. uberis*) can be found. They are generally considered opportunistic invaders that exacerbate existing lung damage.

Fusobacterium necrophorum: More commonly associated with liver abscesses and foot rot, it can sometimes be isolated from pneumonic lungs, particularly in advanced cases with necrotic tissue, where it contributes to tissue destruction.

Staphylococcus aureus: An opportunistic pathogen that can be involved in sporadic cases, often secondary to significant epithelial damage.

2.4.2. Viral Coinfections and Predisposition

Viral infections are critical predisposing factors that significantly increase the susceptibility of cattle to secondary bacterial infections, which are the primary cause of morbidity and mortality in BRD. Viruses commonly implicated in BRD, such as *Bovine Viral Diarrhea Virus* (formerly *Pestivirus bovis* - BVDV), Bovine Herpesvirus 1 (BoHV-1), Parainfluenza-3 Virus (PI-3V), and Bovine Respiratory Syncytial Virus (BRSV), compromise the host's respiratory defenses through various mechanisms. These mechanisms include direct damage to the respiratory epithelium, impairing the mucociliary escalator, and inducing immunosuppression, thereby creating an environment conducive for bacterial proliferation and invasion. For instance, BVDV is well-known for its immunosuppressive effects, which can significantly reduce the animal's ability to mount an effective immune response against bacterial pathogens. Similarly, BoHV-1 and BRSV can cause extensive damage to the tracheal and bronchial epithelium, leading to loss of ciliary function and increased adherence sites for bacteria. This synergistic interaction between viral and bacterial pathogens often results in more severe clinical signs, complicated disease progression, and reduced efficacy of antimicrobial treatments compared to infections with either pathogen alone. Moreover, primary viral infections can exacerbate the pathogenicity of subsequent viral infections, although the specific mechanisms for many viral coinfections remain to be fully elucidated [6].

3. Pathogenesis and Immunology

A comprehensive understanding of the pathogenesis and immunology of BRD is paramount for developing effective diagnostic, preventative, and therapeutic strategies. BRD is a complex multifactorial disease, where the interplay between various bacterial and viral pathogens, as

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previously discussed, orchestrates a cascade of events leading to severe respiratory compromise (Table 1). This section elucidates the intricate mechanisms by which these pathogens initiate and sustain infection, the host's subsequent immune responses, and the various intrinsic and extrinsic factors that ultimately influence disease severity. The pathogenesis of BRD typically begins with viral infections that compromise the host's innate immune defenses, facilitating the colonization and proliferation of opportunistic bacterial pathogens [54]. These initial viral insults often induce a state of immunosuppression, characterized by leukocyte depletion, impaired phagocytic function, and dysregulation of cytokine signaling, thereby creating an environment conducive for secondary bacterial colonization and replication [3]. This initial viral infection can interfere with the mucociliary clearance of the upper respiratory tract and dysregulate tracheal antimicrobial peptides, further weakening the respiratory innate defenses and enhancing the severity of a secondary bacterial infection [55]. Specifically, viral infections can cause erosion of the mucosa, which creates a more accessible entry point for bacterial pathogens, even in areas where the mucosa was previously intact [11]. This compromise of the epithelial barrier, coupled with viral-induced immunosuppression, subsequently enables bacterial agents like *M. haemolytica*, *P. multocida*, *H. somni*, and *M. bovis* to proliferate in the upper respiratory tract and translocate into the lower respiratory tract, initiating bacterial pneumonia [4,6]. Furthermore, certain bacterial species, such as *P. haemolytica*, actively contribute to this impairment by producing cytotoxins that directly target and degrade phagocytic cells, thereby exacerbating the host's inability to clear the infection [56]. Moreover, *M. haemolytica* and *P. multocida* employ toxins and extracellular components to destroy phagocytes, thereby impeding phagocytosis and releasing reactive oxygen metabolites that intensify pulmonary inflammation [57]. This polymicrobial etiology makes BRD a complex disease, as evidenced by studies detecting multiple respiratory pathogens in a high percentage of clinical samples [6,11].

Table 1. Main characteristics of primary bacterial pathogens in BRD.

Pathogen	Taxonomy	Key Virulence Factors	Clinical/Pathological Features	Treatment & Notes
Mannheimia haemolytica	*Pasteurellaceae* Gram-negative	Leukotoxin (*Lkt*), capsule, adhesins, LPS	Acute fibrinous pleuropneumonia, necrotizing inflammation, high mortality in feedlots	Florfenicol, ceftiofur, tulathromycin; leukotoxoid vaccines available but variable efficacy
Pasteurella multocida	*Pasteurellaceae* Gram-negative	Capsule (serotype A:3 most common in BRD), LPS, adhesins	Fibrinopurulent bronchopneumonia, hemorrhages, neutrophil infiltration	Amoxicillin, tilmicosin, florfenicol; rising resistance; bacterin vaccines often combined with viral antigens
Histophilus somni	*Pasteurellaceae* Gram-negative	Biofilm formation, LOS, Ig-binding proteins	Systemic spread possible (septicemia, myocarditis, encephalitis); fibrinous pleuritis & bronchopneumonia	Florfenicol, broad-spectrum antibiotics; bacterins show limited protection; no serotype classification
Mycoplasma bovis	*Mycoplasmataceae* lack cell wall	Surface protein variation, intracellular persistence, biofilm	Chronic pneumonia with caseous necrosis, mastitis, otitis; often complicates mixed infections	Intrinsically resistant to β-lactams; macrolides, tetracyclines; vaccines reduce severity but do not prevent infection

LPS: Lipopolysaccharide; LOS: Lipo-oligosaccharide.

3.1. Mechanisms of Infection

The initiation and perpetuation of BRD involve a complex interplay of virulence factors employed by bacterial and viral pathogens to overcome host defenses and establish infection. At the

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outset, bacterial pathogens, such as *M. haemolytica*, *H. somni*, and *M. bovis*, must first adhere to the respiratory epithelium, often utilizing specific adhesins to colonize the upper and lower respiratory tracts. *M. haemolytica*, for instance, employs adhesins to attach to bovine lung tissue, while its polysaccharide capsule provides protection against phagocytosis and complement-mediated lysis, enabling sustained colonization.

Following adhesion, these bacteria unleash an array of virulence factors. *M. haemolytica* is particularly notable for its leukotoxin, a pore-forming toxin that specifically targets ruminant leukocytes, leading to their apoptosis or necrosis. This not only impairs the host's primary immune response but also releases pro-inflammatory mediators, exacerbating lung inflammation and tissue damage. Furthermore, its ability to induce ciliary stasis disrupts the mucociliary escalator, a crucial innate defense mechanism, allowing bacterial proliferation and deeper penetration into the respiratory system. Similarly, *H. somni* produces lipo-oligosaccharide and can form biofilms, which contribute to immune evasion and persistent infection. It also causes direct damage to the respiratory epithelium and is associated with vasculitis and thrombosis, leading to severe pneumonia and systemic manifestations. *M. bovis*, lacking a cell wall, exhibits unique mechanisms, including intracellular persistence and high antigenic variability of its surface glycoproteins, which allow it to effectively evade both antibiotic treatment and the host immune system, making eradication challenging. Its presence can significantly exacerbate the severity of respiratory disease, leading to increased morbidity and mortality.

A critical element in BRD pathogenesis is the predisposing and often devastating role of viral infections. Viruses such as BVDV, BoHV-1, PI-3V, and BRSV initiate infection by directly damaging the respiratory epithelium. This damage profoundly compromises the integrity of the airway lining, impairs the mucociliary escalator, and creates an ideal environment conducive for bacterial adherence and proliferation [4,11]. BVDV is a potent immunosuppressive agent, significantly reducing the animal's capacity to mount an effective immune response against subsequent bacterial invaders through mechanisms such as leukocyte depletion, neutrophil dysfunction, and impaired cytokine signaling [3,58]. BoHV-1 and BRSV also cause extensive damage to the tracheal and bronchial epithelium, leading to ciliary dysfunction and increasing the availability of attachment sites for bacteria. This synergistic interaction between viral-induced tissue damage and profound immunosuppression, further compounded by bacterial virulence factors, results in more severe clinical signs, complicated disease progression, and often a significantly reduced efficacy of antimicrobial treatments compared to infections with either pathogen alone [6,56]. This profound viral-induced immunosuppression establishes a critical “window of susceptibility”, enabling normally commensal bacteria, such as *M. haemolytica*, *P. multocida*, and *H. somni*, to transform into aggressive opportunistic pathogens capable of initiating severe and often intractable secondary bacterial pneumonia [11]. This is characterized by a necrotizing inflammatory response and progressive fibrinous bronchopneumonia [11,59]. The resultant persistent inflammation and extensive tissue damage not only critically impede host recovery but also markedly heighten the propensity for chronic lung lesions and irreversible pulmonary dysfunction, as viral infections can directly damage lung parenchyma and suppress immune responses [60]. This intricate pathogenic synergy profoundly amplifies morbidity, mortality, and the substantial economic burden on livestock production, underscoring why BRD often presents as a complex, multifactorial challenge [6]. Among bacterial pathogens, *M. haemolytica* and *P. multocida* are frequently identified as primary bacterial infectious agents in BRD etiology, while *M. bovis* is a prominent mycoplasmal factor often isolated from BRD cases [61]. The heightened pathogenicity of *M. haemolytica* is amplified by prior viral infections, leading to an acute form of BRD characterized by significant bacterial adherence to bronchial epithelial cells and progressive inflammation, culminating in fibrinous bronchopneumonia [11].

3.2. Host Immune Responses

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The bovine immune system mounts a multifaceted response to BRD pathogens, involving both innate and adaptive mechanisms to clear infection and mitigate tissue damage. Initially, epithelial cells and immune sentinel cells lining the respiratory tract secrete pro-inflammatory cytokines, initiating a rapid innate response that involves the recruitment of neutrophils, which play a crucial role in eliminating pathogens but can also contribute to lung tissue damage through excessive inflammation [62]. Concurrently, macrophages and dendritic cells phagocytose pathogens, process antigens, and present them to lymphocytes, thus bridging the innate and adaptive arms of immunity [61]. Viral infections, such as those caused by BVDV, can significantly impair these early immune responses by directly suppressing leukocyte function and inhibiting interferon production, thus exacerbating susceptibility to secondary bacterial infections [6,61]. For instance, BVDV's immunosuppressive nature is a critical factor in its interaction with other viruses and bacteria, particularly in BRD, often causing leukocyte depletion, neutrophil dysfunction, and impaired cytokine signaling [3,58]. This primary viral insult frequently facilitates bacterial superinfections, leading to a more severe disease presentation characterized by extensive lung inflammation and tissue destruction [61]. Furthermore, viral infections not only directly damage respiratory tissues and suppress immunity but also disrupt the delicate balance of the respiratory microbiota, altering its structure and composition [4]. This microbial dysbiosis compromises the host's innate defense mechanisms, which typically rely on a balanced microbiota for immune regulation and protection against opportunistic pathogens [63]. Consequently, this disruption facilitates the proliferation and colonization of pathogenic bacteria, exacerbating the inflammatory response and contributing to the severity of BRD [4,6,11]. This immunocompromise is further compounded by the anaerobic conditions within the lungs, often caused by atelectasis and edema, which diminish the phagocytic capacity of alveolar macrophages, thereby hindering their ability to clear invading bacteria and cellular debris effectively [56]. The resident phagocytes of the lung, primarily alveolar macrophages, normally provide a pivotal defense against bacterial infections, yet their function is significantly impaired during inflammatory processes. Indeed, studies have shown that viral infections induce a functional paralysis of the alveolar macrophage phagocytic system, evidenced by dysfunctions in receptor binding, phagocytic ingestion, phagosome-lysosome fusion, intracellular killing, and bacterial degradation [56].

4. Risk Factors and Epidemiology

4.1. Environmental Factors and Management Practices

Beyond inflicting direct cellular damage, viral pathogens critically undermine the host's immune landscape, fundamentally compromising its capacity to effectively combat subsequent bacterial infections. Specifically, viral infections can drastically deplete or severely impair the critical function of alveolar macrophages and neutrophils, which are indispensable components of innate immunity essential for robust bacterial clearance [57,59]. Furthermore, these viral assaults often precipitate a detrimental shift in cytokine profiles, forcibly suppressing vital protective Th1-mediated responses while inadvertently promoting Th2 responses, which are demonstrably less effective against the aggressive proliferation of bacterial pathogens. This intricate and profound dysregulation compromises both local and systemic immune defenses, thereby prolonging infection and exacerbating tissue pathology, ultimately facilitating rampant bacterial colonization and growth. Consequently, this dire immunological vulnerability inevitably predisposes animals to severe and often intractable secondary bacterial pneumonia, which stands as a major contributor to morbidity and mortality in BRD and significantly complicates therapeutic interventions. Moreover, the stress associated with weaning and transportation further exacerbates this immunosuppression, increasing susceptibility to fatal secondary bacterial infections [59]. For instance, calves subjected to abrupt weaning exhibit significant physiological alterations for several days post-separation, thereby compromising their host responses to various pathogens that contribute to BRD [59]. Additionally, factors such as commingling with cattle from diverse origins in sale barns significantly elevate the

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risk of exposure to various pathogens, thereby increasing the susceptibility of feedlot cattle to BRD compared to those acquired directly from farms or ranches [60]. Environmental stressors, including insufficient ventilation, unsanitary bedding conditions, and overcrowding, further contribute to increased pathogen transmission and heightened susceptibility to infection [6]. These environmental determinants, coupled with management practices such as early weaning, contribute significantly to the overall epidemiological burden of BRD [59].

Compounding these biological factors, management practices such as transportation, which leads to substantial stress, also play a crucial role in the etiology of BRD, earning it the colloquial name "shipping fever" [11]. This stress, arising from factors like commingling, changes in diet, and novel environments, significantly compromises the calf's immune system, making it highly vulnerable to opportunistic pathogens that are often commensal in the upper respiratory tract [60,64]. Furthermore, high population densities, inadequate housing, and rapid fluctuations in temperature and humidity further contribute to environmental stress, exacerbating the impact on animal health and increasing the risk of BRD [65,66]. The complex interplay of these environmental and management-related stressors often collectively suppresses the host immune system, further facilitating pathogen exposure and proliferation, which are critical co-requisites in many BRD outbreaks [67,68].

4.2. Geographical Distribution and Prevalence

A comprehensive understanding of BRD necessitates a detailed description of the geographical distribution and prevalence of bacterial infections across key regions such as Europe, and the rest of the world. Such specific epidemiological data and regional studies are critical for identifying high-risk areas, understanding the spread of specific bacterial strains, assessing the true economic impact, and formulating effective, targeted preventative and therapeutic strategies.

In Europe, BRD is recognized as a major health concern in the cattle industry, leading to significant morbidity and mortality and consequently, widespread antimicrobial use [69]. As discussed above the bacterial pathogens most frequently identified in association with BRD across Europe include *M. haemolytica, P. multocida, H. somni*, and *M. bovis*. These species are commonly found as commensals in the upper respiratory tract of cattle but can proliferate and cause disease during periods of stress or viral infection. BRD has a high impact on European cattle farming, particularly in beef production. The identification of these prevalent pathogens in European BRD cases underscores their likely significant contribution to the disease burden within herds [69].

Regional and global studies highlight the prevalence and distribution of these key bacterial pathogens:

- ***Pasteurella multocida***: This pathogen is a prevalent commensal and opportunistic pathogen worldwide, possessing a broad host range [70]. Eleven European studies have specifically investigated *P. multocida* isolates in cattle, with German surveillance from 2014 to 2018 consistently reporting its isolation from respiratory disease cases. In Asia, four studies have focused on *P. multocida*, and eight studies have been conducted in North America [71].
- ***Mannheimia haemolytica***: Recognized as a primary etiological agent of BRD globally [72,74], *M. haemolytica* is the predominant bacterial pathogen isolated from BRD cases worldwide [72]. Fatal *M. haemolytica* infections have been documented in the Netherlands [75], and its serovars associated with respiratory disease have been characterized in Great Britain [76]. Surveillance data from Germany also includes *M. haemolytica* isolates from respiratory disease [71]. Studies from North America highlight its significant role in BRD morbidity and mortality [71]. In Africa, *M. haemolytica* has been identified as a principal cause of pneumonic pasteurellosis in small ruminants in Ethiopia [77].
- ***Histophilus somni***: This pathogen is an important bacterial contributor to the multifactorial etiology of BRD globally [1,78,79]. European studies include investigations into *H. somni* isolates [71], and it is a key bacterial player in North American BRD cases [80,81].

 doi:10.20944/preprints202512.0400.v1

- ***Mycoplasma bovis***: This pathogen is widespread in cattle industries across the globe [82]. It has spread to many countries and is endemic in Europe, having been first isolated in the USA in 1961 and in Denmark in 1981 [83]. It is known to be prevalent in countries such as France, Finland, the UK, and the Netherlands [84], and is the most frequently identified *Mycoplasma* species associated with respiratory disease in cattle in England and Wales [85]. Globally, five European studies, one Asian study, and two North American studies have focused on *M. bovis* isolates [71]. Its introduction has also been recorded in Oceania, specifically New Zealand, in 2017 [86].

Collectively, BRD poses a significant challenge globally, leading to substantial economic losses in the cattle industry [1,6,87]. In North America, BRD accounts for approximately 75% of all disease incidence and 50% of all mortality in cattle farms, with an even higher prevalence (nearly 90%) in calves [88]. The complex interplay of these bacterial pathogens underscores the need for continuous, region-specific epidemiological surveillance to effectively manage and mitigate the disease worldwide.

5. Clinical Manifestations and Diagnosis

5.1. Clinical Signs

The clinical manifestations characteristic of bovine respiratory infections, particularly those caused by key bacterial pathogens such as *P. multocida*, *M. haemolytica*, *M. bovis*, and *H. somni*, are highly diverse and often non-specific. This is largely due to their nature as opportunistic pathogens, frequently existing as commensals in the upper respiratory tract of cattle [4,67,69,72]. Their transition to pathogenicity is typically triggered by predisposing factors such as environmental stressors or viral co-infections, which compromise the host's immune system and respiratory defenses [4,67,72]. This multifactorial etiology significantly contributes to the broad and often overlapping clinical signs observed in BRD [1,69], thereby necessitating precise identification for accurate diagnosis and effective management. Diagnosis of BRD often relies on observing clinical signs such as fever, cough, and nasal discharge, which necessitates skilled personnel for accurate detection [1]. However, these clinical signs are not pathognomonic for BRD and can be indicative of other disease conditions, highlighting the limitations of diagnosis based solely on observable symptoms. Therefore, advanced diagnostic methods, including molecular and serological assays, are crucial for differentiating between the various bacterial and viral pathogens involved in BRD and for implementing targeted interventions [1].

5.2. Diagnostic Techniques

The clinical manifestations characteristic of bovine respiratory infections are highly diverse and often non-specific, largely due to their nature as opportunistic pathogens and the multifactorial etiology of BRD [1,4,67,69,72]. While observation of clinical signs like fever, cough, and nasal discharge is a primary diagnostic approach, these symptoms are not pathognomonic and can overlap with other conditions, limiting diagnosis based solely on observable symptoms [1]. Therefore, to overcome these limitations and enable precise identification and targeted interventions, advanced diagnostic methods are crucial for differentiating between the various bacterial and viral pathogens involved in BRD [1]. These methods provide specific information beyond clinical observation, which is vital for effective management and treatment.

5.3. Molecular Diagnostics

Molecular techniques, such as Polymerase Chain Reaction and quantitative PCR (qPCR), offer rapid, highly sensitive, and specific detection of both bacterial and viral pathogens. These methods are particularly advantageous for identifying fastidious or difficult-to-culture organisms, like *M. bovis*, which is frequently identified using molecular approaches [85]. Molecular diagnostics allow for

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the differentiation of specific strains and co-infections, providing a clear etiological picture essential for targeted therapy. Moreover, the integration of novel diagnostic platforms, such as GeneXpert, allows for multiplexed detection of a broad spectrum of pathogens, enhancing both sensitivity and coverage. This capability is particularly beneficial in cases where rapid, on-site diagnostics are required to inform immediate treatment decisions and prevent widespread disease transmission [89]. These molecular approaches have significantly improved upon traditional diagnostic methods by offering enhanced precision and speed in pathogen identification [61,90]. However, despite these advances, targeted qPCR diagnostics for BRD still face challenges, primarily due to the vast number of potential bacterial and viral pathogens involved, making comprehensive screening economically and logistically unfeasible for routine application [91]. Newer diagnostic methods such as 16S rRNA gene amplicon sequencing and Oxford Nanopore MinION Sequencing are now being utilized for identifying both known and novel bacterial and viral agents causing BRD, offering advantages in speed and comprehensiveness over traditional methods [92]. These advanced molecular and metagenomic sequencing techniques enable the simultaneous identification of multiple pathogens, including those that are difficult to cultivate, thereby providing a more complete understanding of the polymicrobial nature of BRD and informing more precise antimicrobial interventions [93]. Furthermore, current diagnostic strategies relying on clinical sign observation necessitate skilled personnel and often lack standardization, complicating accurate diagnosis and treatment [1].

5.4. Serological Assays

Serological assays, including Enzyme-Linked Immunosorbent Assays, detect the presence of antibodies against specific BRD pathogens. These assays are invaluable for assessing an animal's or herd's exposure status, monitoring vaccine efficacy, and conducting comprehensive epidemiological studies. By providing critical insights into herd health dynamics and pathogen prevalence [1], serology is essential for guiding preventative and control measures. For instance, ELISA techniques are widely utilized for detecting specific antiviral antibodies, including those against BVDV, BoHV-1, PI-3V, and BRSV [61]. However, a significant limitation of serological assays is their inability to differentiate between antibodies resulting from natural infection and those induced by vaccination. This inherent ambiguity can complicate the interpretation of results, particularly in vaccinated populations, and may obscure the true extent of field exposure or vaccine breakthrough. This necessitates integrating serological data with other diagnostic modalities, such as molecular assays or clinical observations, to achieve a more conclusive diagnosis and to effectively monitor disease status within a herd [74].

5.5. Bacteriological Culture and Antimicrobial Susceptibility Testing

For bacterial pathogens, conventional bacteriological culture remains fundamental for isolating and identifying the specific causative agents. Once isolated, antimicrobial susceptibility testing is performed to determine the effectiveness of various antibiotics against the identified bacteria. This step is essential before initiating antimicrobial therapy to ensure the selection of an effective drug and to mitigate the development of antimicrobial resistance. The identification of the causative agent and antibiotic susceptibility testing are crucial steps for informing appropriate treatment strategies. Despite the foundational role of culture-based methods, their utility is somewhat limited by the time required for bacterial growth and identification, which can delay the initiation of targeted antimicrobial interventions. Moreover, the sensitivity of these traditional culture techniques is often lower than that of molecular tools, potentially leading to missed organisms due to handling or inherent limitations [94]. This underscores the critical need for a diagnostic paradigm shift towards rapid, multiplexed molecular approaches that can overcome these inherent limitations, particularly for fastidious bacteria [61]. However, standard bacteriological culture and qPCR methods for identifying bacterial and mycoplasmal pathogens still play a significant role in diagnostic laboratories [95]. However, the increasing complexity of polymicrobial infections and the emergence of

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antimicrobial resistance necessitate a comprehensive approach that integrates phenotypic and genotypic characterization for more precise diagnostics and therapeutic strategies [74].

The integration of these advanced diagnostic methods enables a comprehensive understanding of the BRD etiology in affected animals, facilitating precise diagnosis, differentiation of pathogens, and the implementation of targeted and effective interventions [1]. This shift from symptomatic treatment to pathogen-specific management is critical for improving animal health outcomes and reducing the economic impact of BRD.

5.6. Differential Diagnosis

The differential diagnosis for BRD must encompass a range of bacterial and viral pathogens. Key bacterial agents include *M. haemolytica*, *P. multocida*, *H. somni*, and *M. bovis* [1], all frequently implicated in the polymicrobial nature of BRD. Essential viral pathogens to consider are BVDV, BoHV-1, PI-3 virus, and BRSV [61], with emerging pathogens such as Influenza D virus also warranting consideration [91]. Furthermore, recent metagenomic analyses have broadened this scope to include *Bovine Rhinitis A* and *B viruses* as contributors to BRD, underscoring the dynamic and evolving understanding of the disease's viral etiology [96]. The intricate interplay between these bacterial and viral agents, coupled with environmental stressors such as overcrowding and poor ventilation, significantly contributes to the complex pathogenesis of BRD [1]. It is critical to distinguish BRD from aspiration pneumonia, which can arise from improper feeding practices, and purely viral pneumonias as misdiagnosis can lead to ineffective treatment strategies [61]. Accurate differentiation among these conditions is crucial for guiding appropriate therapeutic interventions and preventing the widespread use of antimicrobials where viral etiologies dominate [61]. Moreover, the clinical presentation of BRD is highly variable, often necessitating antemortem diagnoses without clear etiological identification [97]. Despite advancements, the multifactorial nature of BRD, involving host, environmental, and etiological factors, continues to challenge the development of definitive diagnostic and prognostic models [1,97].

6. Treatment and Management Strategies

6.1. Antimicrobial Therapy

Antibiotics are conventionally employed as a primary treatment for bacterial components of BRD; however, the emergence of antimicrobial resistance poses a significant concern for their continued efficacy [1]. Consequently, judicious antibiotic stewardship is imperative, involving the selection of appropriate antimicrobial agents based on susceptibility testing and the implementation of responsible dosing regimens [13]. Commonly used classes include macrolides, tetracyclines, cephalosporins, and, in severe cases, fluoroquinolones, although the escalating resistance to these agents necessitates careful consideration and often limits their utility [3]. Empirical antimicrobial therapy, which frequently includes penicillins, tetracyclines, macrolides, and quinolones, is often initiated due to the polymicrobial nature of BRD development [98]. Despite their broad-spectrum activity, the indiscriminate use of these antibiotics can contribute to the selection of resistant bacterial strains, thereby diminishing their long-term effectiveness [61]. This underscores the urgent need for novel antimicrobial agents and alternative therapeutic strategies to combat the rising prevalence of multidrug-resistant pathogens in BRD [2]. The administration of antimicrobials can be categorized into therapeutic or preventative approaches, with preventative use further delineated into prophylactic and metaphylactic applications [99]. Prophylactic administration aims to prevent disease before any clinical signs appear, typically in animals at high risk, while metaphylactic treatment involves administering antimicrobials to an entire group when a certain percentage of animals within that group show clinical signs of BRD, thereby controlling the spread of infection and reducing morbidity and mortality [100]. However, evidence suggests that mass medication with antimicrobials provides inconsistent control of BRD and raises concerns regarding the emergence of antimicrobial resistance [101]. Despite considerable resources invested in developing new

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technologies and management strategies to mitigate BRD, the incidence of morbidity and mortality has remained relatively constant over the past 45 years [102]. This stability suggests that current prophylactic and metaphylactic strategies, while widely implemented, may not be adequately addressing the complex pathogenesis of BRD, or that the resistance patterns of common pathogens are rapidly eroding their efficacy [100]. Consequently, this necessitates a critical re-evaluation of current treatment protocols and an increased focus on alternative therapies and preventive measures [103]. Despite the widespread initiatives encouraging responsible antimicrobial use in veterinary medicine, the economic burden and welfare concerns associated with chronic respiratory infections persist, often exacerbated by the polymicrobial nature of BRD and the potential for antimicrobial resistance [81,104]. This necessitates further exploration into the complex dynamics of antimicrobial resistance development in feedlot settings, particularly given the increased resistance to enrofloxacin, florfenicol, and macrolides observed after metaphylactic treatments compared to unexposed bacteria [105]. However, two meta-analyses examining metaphylaxis in beef cattle have yielded conflicting results regarding the comparative efficacy of macrolides versus tetracyclines, highlighting the need for more targeted research to identify specific circumstances where these antimicrobials are most effective [106].

6.2. Supportive Care

Supportive care strategies play a crucial adjunctive role in managing BRD, focusing on alleviating symptoms, bolstering the animal's natural defenses, and promoting recovery. These interventions include providing adequate hydration, nutritional support to maintain energy levels, and anti-inflammatory medications to reduce fever and discomfort, thereby improving overall animal welfare and facilitating a quicker return to productivity. While non-steroidal anti-inflammatory drugs such as flunixin meglumine are commonly used to mitigate inflammation and pain, their efficacy as a monotherapy for BRD is limited, underscoring the need for their integration within a comprehensive treatment regimen [71]. Furthermore, novel research indicates that certain plant-based therapeutics, such as essential oils, may offer a promising alternative or supplementary approach to conventional treatments, potentially mitigating inflammation and possessing antimicrobial properties against BRD pathogens [3]. However, further research is required to ascertain the effects of essential oils on the respiratory commensal microbiota of cattle and to evaluate their cytotoxicity on the lower respiratory tract [60]. Furthermore, the development of nasal-delivered probiotics and essential oils offers a targeted approach to inhibit pathogenic bacteria with minimal disruption to commensal flora, representing a significant advancement in alternative BRD management strategies [4,105]. Additionally, studies have demonstrated that certain *Lactobacillus* strains, specifically those isolated from the nasopharynx of healthy feedlot cattle, exhibit in vitro antimicrobial activity against key BRD pathogens such as *M. haemolytica* [29]. Further investigations have shown that intranasal inoculation of *Lactobacillus* spp. can inhibit the colonization of *M. haemolytica* in the nasopharynx of dairy calves, suggesting their potential as a probiotic intervention to mitigate BRD bacterial pathogens in feedlot cattle [4]. Similarly, plant-based therapeutics, including essential oils like thymol and carvacrol, have demonstrated synergistic effects with conventional antibiotics by disrupting bacterial membranes and enhancing drug penetration [3]. Moreover, a single intranasal application of essential oil spray has been shown to modulate the bovine respiratory microbiome, suggesting its potential to mitigate BRD as an alternative to antimicrobial metaphylaxis. This approach provides a targeted intervention that could reduce the reliance on systemic antibiotics, thereby decreasing the risk of antimicrobial resistance development [4,105]. Further investigation into plant-based therapeutics, or phytotherapy, reveals a growing recognition of their potential as environmentally friendly and efficient alternatives for preventing and managing bovine diseases [3]. However, comprehensive toxicological data for many plant-based therapeutics, including essential oils, remains largely absent, posing risks of inadvertent toxicity or treatment failure without standardized safety testing for residues, interactions, and toxic thresholds.

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6.3. Prevention and Control Measures

Effective prevention and control measures are critical for mitigating the substantial economic and welfare burdens associated with BRD, particularly given the challenges posed by antimicrobial resistance. These measures encompass vaccination programs, optimized management practices to reduce stress, and the implementation of robust biosecurity protocols to minimize pathogen transmission within herds [4]. However, the multifactorial epidemiology of BRD, involving complex interactions between host, environmental, and microbial factors, often renders conventional control strategies insufficient, necessitating a holistic and integrated approach to disease management [2]. This includes the careful selection of antimicrobial agents based on resistance surveillance, alongside strategic metaphylaxis to target high-risk groups rather than widespread, undifferentiated treatment. Additionally, the development of novel anti-virulence strategies targeting bacterial pathogenicity mechanisms, rather than growth, could offer a promising avenue to reduce selective pressure for antimicrobial resistance [4]. Furthermore, non-antimicrobial alternatives, such as bacteriophages and immunomodulatory agents, are being explored to augment host defenses and directly combat pathogens without contributing to resistance development. The One Health approach, which recognizes the interconnectedness of human, animal, and environmental health, is increasingly being adopted to address the complex challenges of BRD by integrating strategies that consider these interdependencies. This holistic framework emphasizes interdisciplinary collaboration and shared responsibility in developing sustainable solutions for bovine respiratory health. This integrated perspective, encompassing animal welfare and broader ecological contexts, is crucial given the complexity of viral communities and the emergence of novel pathogens. Such collaborative efforts, involving veterinary academic institutions, private practitioners, and pharmaceutical industries, enable a more robust response to health crises by fostering shared knowledge and resources across sectors.

7. Impacts of Bacterial Bovine Respiratory Disease

7.1. Economic Impact

BRD imposes significant economic burdens on the global cattle industry due to direct costs associated with treatment, mortality, and production losses, as well as indirect costs related to antimicrobial resistance and reduced market access [107]. The substantial financial impact of BRD, particularly within intensive livestock operations like feedlots, is further exacerbated by the widespread use of antibiotics, which raises concerns regarding antimicrobial resistance and trade implications [3]. Moreover, the economic burden extends to public health concerns, given the potential for transferable resistance genes in BRD pathogens to spread to zoonotic bacteria, posing a threat to human health [4]. The economic ramifications of BRD also extend to indirect costs such as reduced carcass quality, decreased feed efficiency, and increased labor requirements, significantly impacting the overall profitability and sustainability of beef and dairy production [3]. Beyond immediate financial losses, these long-term effects compromise the genetic potential of affected herds and diminish consumer confidence in livestock products [7]. Indeed, the economic toll on the US beef industry alone exceeds $4 billion annually, surpassing the combined financial impact of all other bovine diseases [2]. The economic loss attributed to BRD, including treatment costs, weight loss, and mortality, is estimated to exceed $333 million annually [108]. In Brazil, BRD represents the primary cause of illness in feedlot cattle, accounting for 44.1% and 46.7% of all cases in 2012 and 2013, respectively, with morbidity rates reaching up to 7.05% in some operations [109]. Similarly, in North America, BRD accounts for approximately 30% of total cattle deaths worldwide, with annual economic losses exceeding one billion dollars [61]. This pervasive disease is considered the costliest ailment affecting feedlot cattle, contributing to substantial annual losses [110]. These losses are incurred across various phases of beef production, affecting both pre- and post-weaned calves, and are primarily driven by production decrements, treatment expenditures, and increased animal mortality [111]. BRD is a leading cause of morbidity and mortality in feedlot cattle, accounting for up

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to 80% of illnesses and nearly 50% of fatalities in some operations, thereby creating significant economic losses [3]. This substantial economic impact underscores the urgent need for effective prevention and control strategies to mitigate both the financial burden and the significant animal welfare challenges posed by BRD [15,61,112].

7.2. Animal Welfare Implications

The suffering endured by affected animals, encompassing symptoms such as coughing, fever, and dyspnea, raises ethical concerns regarding animal husbandry practices and necessitates comprehensive welfare-oriented management strategies [92]. Beyond the overt clinical signs, chronic pain, stress, and reduced quality of life associated with BRD can have lasting impacts on an animal's well-being, even after recovery [101]. These welfare implications are compounded by the necessity of repeated handling and treatments, which can further elevate stress levels and compromise the immune response of already compromised animals [113]. The prolonged recovery periods and potential for permanent lung damage also contribute to a diminished welfare state, often leading to early culling [6]. The subclinical forms of BRD, which are often difficult to detect, also contribute to poor animal welfare by causing chronic discomfort and hindering normal physiological functions without displaying overt signs [61,114]. Furthermore, the psychological stress associated with social disruption and isolation during treatment can exacerbate an animal's distress, highlighting the need for holistic welfare considerations [66].

7.3. Public Health Concerns (Antimicrobial Resistance)

Beyond the direct impact on cattle health and producer economics, BRD also presents significant public health concerns, primarily through the potential for zoonotic disease transmission and the exacerbation of antimicrobial resistance (AMR). The extensive use of antibiotics in BRD treatment contributes to the development and spread of resistant bacterial strains, potentially compromising the efficacy of these drugs in both veterinary and human medicine. The widespread use of antibiotics to combat BRD, particularly in intensive livestock operations, has profound public health implications, primarily due to the acceleration of antimicrobial resistance. This concern is compounded by the fact that resistant bacteria can transfer from animals to humans through direct contact, cross-contamination, or the food chain, thereby contributing to a global public health crisis [3]. The emergence of AMR in BRD pathogens is not merely an animal health issue; it poses a direct threat to human health because resistant genes within these pathogens can spread to zoonotic bacteria via self-transmissible conjugative elements. This genetic exchange means that resistance can be transferred not only between BRD-related bacteria but also to other non-BRD pathogens, such as *E. coli* [4]. Consequently, the high consumption of antibiotics for BRD treatment fuels the development of drug-resistant strains in cattle, which can then impact human populations indirectly through the food chain, water, air, and agricultural practices like the use of manured and sludge-fertilized soils [6]. This interconnectedness underscores the critical need for counteracting measures to reduce the development and spread of AMR in BRD pathogens to safeguard both animal and human health [2,4]. The economic and trade implications are also significant, as nations with frequent incidence or weak control policies risk losing market access due to global concerns regarding animal welfare and antimicrobial resistance [3]. Furthermore, the potential for transferable elements carrying resistance genes to move from BRD pathogens into zoonotic pathogens presents a direct public health threat [4]. Despite these economic losses, reducing the prevalence of BRD could lead to net societal gains in the United States, as benefits from lower beef prices would outweigh increased costs in other protein markets [113]. The judicious implementation of mitigation strategies, such as the separation of veterinary and human antimicrobials, alongside improved hygiene practices, could significantly curtail the propagation of antimicrobial resistance [115]. From an economic perspective, the negative externalities associated with antimicrobial use in livestock production, particularly in the context of BRD, necessitate a comprehensive assessment of its total economic value, extending beyond direct healthcare costs to include agricultural productivity and international trade disruptions [116,117].

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8. Future Directions and Research Gaps

8.1. Novel Diagnostic Tools

The development of advanced diagnostic tools is crucial for the early and accurate identification of BRD pathogens. This enables targeted treatment strategies and reduces the need for empirical antimicrobial use. Current diagnostic limitations, such as the time required for bacterial culture and antimicrobial susceptibility testing, often delay appropriate therapeutic interventions, leading to suboptimal outcomes and increased selective pressure for resistance [118]. Point-of-care diagnostics, leveraging molecular techniques or biosensors, could provide rapid and precise pathogen identification, thereby facilitating timely and effective antimicrobial stewardship [117]. For instance, untargeted nanopore sequencing on portable devices like the MinION Mk1B offers the potential for rapid, simultaneous identification of viral and bacterial BRD pathogens directly on farms, allowing for more prudent antibiotic usage [92]. Furthermore, the introduction of a new technology, C-FISH, supported by artificial intelligence, although still only tested on humans and horses, could be of great help in diagnosing pathogens with high accuracy. This technology is also capable of performing antibiotic sensitivity tests with MIC values in a very short time [119]. Beyond individual pathogen detection, integrating environmental detection techniques into surveillance strategies could significantly enhance early warning systems, particularly for pathogens with environmental reservoirs or shedding. These sophisticated diagnostic capabilities, coupled with enhanced surveillance, will enable the timely identification of emerging pathogen threats and facilitate rapid responses to prevent potential pandemics.

8.2. Vaccine Development

Ongoing research into vaccine development remains paramount for robustly enhancing herd immunity and significantly reducing both the incidence and severity of BRD, thereby fundamentally decreasing the reliance on antimicrobial treatments [98]. The investigation into novel vaccine platforms, including subunit, live attenuated, and vector-based vaccines, is essential for achieving comprehensive and durable protection against the diverse spectrum of BRD pathogens, which frequently involve multiple viral and bacterial agents. Furthermore, concentrated efforts toward developing multivalent vaccines that target several key pathogens simultaneously are crucial, as this approach offers not only extensive protection but also streamlines vaccination protocols for livestock [6]. Such advancements are poised to profoundly reduce the overall disease burden and critically alleviate the selective pressure driving antimicrobial resistance [99]. The dedicated pursuit of novel vaccine adjuvants, vital for enhancing immune responses and prolonging protective immunity, represents another pivotal area of investigation. Ultimately, a robust vaccine development program, meticulously incorporating advanced immunogen design and delivery systems, is indispensable for improving animal welfare and ensuring sustainable livestock production by drastically cutting both disease incidence and the imperative for antimicrobial interventions. Moreover, research into nano-vaccines offers promising avenues for improved protection against respiratory and other diseases in farm animals, potentially leading to substantial benefits in global cattle health and welfare [68]. This is particularly relevant given the emergence of new pathogens and the limitations of current commercial vaccines, which often lack cross-protection against evolving strains [6]. While existing commercial vaccines often demonstrate variable efficacy in mitigating morbidity and mortality from BRD, particularly against diverse viral agents like BVDV and BoHV-1, further optimization and a deeper understanding of the bovine immune response across different ages and production groups are warranted [98]. For instance, modified live vaccines offer robust immunity but demand meticulous handling, whereas killed vaccines, despite being safer, necessitate multiple doses and adjuvants [3]. Nanoparticle-based vaccine platforms, for example, demonstrate potential for enhanced immunogenicity and targeted delivery, addressing some of these limitations [120].

8.3. Alternative Therapies

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The exploration of alternative therapies is crucial for mitigating the widespread reliance on conventional antimicrobial treatments for BRD. Emerging strategies, such as plant-based therapeutics, offer promising avenues for innovative livestock health management [3]. These alternatives are vital for reducing the selection pressure that drives antimicrobial resistance and for promoting sustainable practices in animal agriculture. For example, bacteriophages and antimicrobial peptides represent viable alternatives, demonstrating targeted pathogen destruction and immunomodulatory effects with reduced risk of resistance development [116]. Additionally, the application of immunomodulators, such as phytochemicals derived from botanicals, could enhance the host's natural defenses against respiratory pathogens, thereby minimizing the need for conventional antibiotics [3]. Nutraceuticals and prebiotics also show potential in bolstering gut and respiratory tract immunity, contributing to overall host resilience against BRD. Furthermore, the strategic incorporation of probiotic interventions can modulate the respiratory microbiota, thereby competitively exclude pathogens and fortify mucosal barriers against infectious agents. Phytochemicals from medicinal plants like garlic, turmeric, and neem, as well as essential oils from species such as *Eucalyptus* spp., have demonstrated antimicrobial, antioxidant, and immunomodulatory properties, suggesting their potential to enhance respiratory health and reduce pathogen load in cattle [3]. This diversification of treatment options aligns with a broader strategy of reducing antimicrobial usage, and studies exploring the efficacy of non-antimicrobial interventions, such as preconditioning and optimized bedding, could provide further insights into holistic BRD management [121]. These therapeutics, such as *Azadirachta indica*, *Curcuma longa*, and *Eucalyptus* spp., offer therapeutic activity against key BRD-associated pathogens like *P. multocida*, *M. haemolytica*, and *M. bovis*, while simultaneously presenting a lower risk for antimicrobial resistance development compared to traditional chemical drugs. The significant advantages of plant therapeutics, notably their broad-spectrum antimicrobial activity against bacterial, fungal, viral, and protozoal growth, are increasingly supported by empirical evidence, forming a robust foundation for their integration into veterinary protocols [3].

8.4. Genomic and Proteomic Approaches

Genomic and proteomic approaches, alongside other "omics technologies" like epigenomics and transcriptomics, offer unprecedented opportunities to decipher the complex interplay between host genetics, pathogen virulence, and disease progression in BRD [116]. These methodologies facilitate the identification of novel therapeutic targets and biomarkers for early detection and prognosis. Advanced techniques such as Next-Generation Sequencing are crucial for discovering new pathogens, understanding respiratory pathogenic interactions, and elucidating the mechanisms underlying disease pathogenesis, leading to improved early risk assessment and surveillance programs [6]. Such analyses provide crucial insights into host susceptibility or resistance to BRD by identifying specific genetic markers associated with immune responses and disease outcomes [3]. This enables the development of precision breeding strategies aimed at enhancing genetic resistance to BRD within cattle populations and supports the development of precise and personalized immunotherapies [116]. Further, comparative genomics can identify virulence factors and antibiotic resistance genes in bacterial pathogens, guiding the development of targeted antimicrobials and more effective vaccines [6,122]. Proteomics, on the other hand, allows for the comprehensive analysis of protein expression profiles in response to infection, providing insights into host-pathogen interactions and potential drug targets [92]. This includes the identification of biomarkers for disease progression and vaccine efficacy, allowing for more accurate monitoring and evaluation of intervention strategies. The application of metagenomic approaches also reveals the presence of previously undetected pathogens in bovine lungs, expanding the understanding of BRD's polymicrobial nature [99].

9. Conclusions

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BRD represents one of the diseases with the highest impact in cattle farming, particularly in beef production, constituting a leading cause of morbidity, mortality, and antimicrobial use in cattle [122]. The primary objective should be to adopt comprehensive biosecurity measures and diligent farm management practices to prevent the introduction of pathogens into the herd. Reducing stress is another crucial element; thus, actions such as avoiding long transports, carefully managing weaning and dietary changes, and preventing the co-mingling of animals of different ages can all contribute to reducing disease incidence. Crucially, when BRD appears in a herd, early and accurate diagnosis, identification of the causative agent, and comprehensive antibiotic susceptibility testing are essential before initiating therapy, thereby underpinning responsible antimicrobial stewardship and mitigating the development of resistance.

Generally, in accordance with the Guidelines for the Prudent Use of Antibiotics issued by many Ministry of Health around the world, when selecting the most suitable antibiotic for treating respiratory affections, it is necessary to consider not only laboratory test results but also the likelihood that the chosen molecule will exceed the MIC values for the main pathogenic bacteria (e.g., *M. haemolytica*, *P. multocida*, and *H. somni*) within the lung parenchyma and throughout the respiratory tree. The probability of achieving effective concentrations is higher for florfenicol, ceftiofur, tilmicosin, tulathromycin, and quinolones, but modest for penicillin, ampicillin, amoxicillin, erythromycin, and tylosin. Given the frequent involvement of *Mycoplasma* spp. in respiratory pathology, it is generally preferable to use products active against this microorganism, rather than beta-lactam antibiotics. Parenteral administration of antibiotics is typically preferred over oral administration, as the latter can be ineffective in animals too ill to drink or eat, and it more readily induces resistance compared to parenteral methods. To ensure the active ingredient reaches therapeutic concentrations in the lung and to prevent the emergence of antibiotic resistance, it is advisable not to modify antibiotic therapy before 48 hours from the start of treatment, even if a clinical response is not yet evident. The duration of therapy should be sufficient to allow for full recovery and should not be discontinued until at least 48 hours after clinical remission.

While currently available vaccination products aimed at preventing BRD infection may not offer complete prevention and often require further optimization [98], they consistently yield significant results in reducing the severity of clinical symptoms and, critically, in decreasing the environmental shedding of various etiological agents. This robustly contributes to lowering the environmental bacterial load, reducing animal losses, decreasing management costs, and significantly lessening antibiotic usage, thereby playing a pivotal role in the reduction of antimicrobial resistance [121]. Moreover, strategic integration of diverse vaccine types, including both live and attenuated formulations, targeting primary bacterial and viral pathogens such as *P. multocida*, *M. haemolytica*, BRSV, PI-3V, BVDV, and BoHV-1, is crucial for establishing broad-spectrum immunity within susceptible populations [61]. However, the efficacy of bacterial vaccines against BRD pathogens remains a subject of debate due to inconsistent field performance, often leading to their less frequent adoption in feedlots compared to viral vaccines [2,123].

Future Perspectives and Take-Home Massages

The continued global significance of Bovine Respiratory Disease, despite concerted research and management efforts, underlines the fact that conventional approaches are reaching their limits. The polymicrobial and multifactorial nature of BRD demands a paradigm shift from reactive, antibiotic-oriented treatment to proactive, integrated, and precision-based management strategies. Key messages from this review emphasize that progress in effective control depends on disrupting the interrelated chain of events resulting from stress, viral infection, and bacterial proliferation. Accordingly, future efforts must be directed into several crucial and interlinked domains.

1. Advanced Diagnostics and Precision Medicine: Accurate and timely diagnosis provides the future for BRD control. Beyond subjective clinical scoring, research efforts should focus on the validation and commercialization of rapid, pen-side diagnostic tools. Potential examples could include:

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Multiplex Pathogen Detection: Devices that can simultaneously identify a panel of major viral and bacterial pathogens from a single nasal swab to inform etiology-specific treatment decisions.

Host-Specific Biomarkers: Development and use of biomarkers (for example, acute phase proteins like haptoglobin, or specific microRNAs) present in blood or saliva capable of objectively identifying animals in the early subclinical stage of disease, predict the severity, and differentiate bacterial from viral infections.

Antimicrobial Susceptibility Testing at the Point of Care: Development of rapid tests to guide antibiotic choice at the individual or group level, contributing to combating AMR through good antimicrobial stewardship.

2. Next-Generation Vaccinology: Though vaccines are available, their efficacies vary. The next generation in vaccinology should study:

Universal Viral Vaccines: Development of vaccines that target conserved epitopes across viral strains for the induction of broader and longer-lasting immunity against primary initiators such as BVDV, BRSV, and BoHV-1.

Pathoblocker and Subunit Vaccines: For bacterial agents such as *M. haemolytica*, it may be more productive to develop vaccines targeting important virulence factors rather than the whole bacterium. Such "pathoblocker" vaccines could prevent disease without driving bacterial clearance and, by extension, reduce selection pressure for resistance.

Mucosal Delivery Platforms: This approach enhances mucosal immunity via intranasal or oral vaccines, providing a strong first line of defense at the primary site of infection.

3. Sustainable Therapeutics and Antibiotics Alternatives: Overuse is unsustainable. Some promising alternatives requiring intensive research include:

Phage Therapy: The application of bacteriophages in a targeted manner to lyse specific BRD-associated bacteria, thus providing a very specific alternative to broad-spectrum antibiotics.

Immunomodulators and Host-Directed Therapies: Development of compounds that enhance the innate immune response of the host, like interferons or other innate immune stimulants, to better clear infections in cattle without direct antimicrobial pressure.

Anti-Virulence Compounds: Agents that disarm pathogens by inhibiting toxin production, biofilm formation, or *quorum-sensing* to render them less harmful without killing them, thereby minimizing resistance development.

Plant-Based Therapeutics and Essential Oils: As identified in the latest research, standardized and formulated plant-derived compounds with known antimicrobial, anti-biofilm, and immunomodulatory properties represent a natural armamentarium for prevention and adjuvant therapy.

4. Data Integration and Predictive Analytics: "Big Data" from automated monitoring systems - infrared thermography for fever, accelerometers for activity, and Radio Frequency Identification (RFID) feeders for intake - will revolutionize BRD management. Integrating real-time zootechnical data with information on pathogens and biomarkers through machine learning algorithms will enable the construction of early warning systems to predict BRD outbreaks before clinical signs appear, thus offering the possibility of pre-emptive intervention.

In conclusion, the battle against BRD is evolving from a simple war of attrition using antibiotics to a sophisticated campaign requiring intelligence - that is, advanced diagnostics-specialized special forces, or novel vaccines and therapeutics - and a strong home-front defense - or optimized management and nutrition. There is a dire need for a collaborative approach that unites microbiologists, immunologists, clinicians, data scientists, and farmers. Embracing these future perspectives will enable the cattle industry to move toward a more sustainable, effective, welfare-focused control of this devastating disease complex.

Author Contributions: Conceptualization, V.C., C.S. and S.P.; investigation, A.-R. A. and C.S.; writing—original draft preparation, C.S.; writing—review and editing, V.C. and S.P.; visualization,

 doi:10.20944/preprints202512.0400.v1

A.-R. A.; supervision, Y.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Acknowledgments: The authors would like to thank Ennio Cuteri and Fluence Group for creating the graphic abstract, generated using the AI Gemini 3 pro image preview tool. The authors have reviewed and edited the output and take full responsibility for the content of this publication.

Conflicts of Interest: The authors declare no conflicts of interest.

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