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Bovine coronavirus in the One Health framework: Zoonotic potential, molecular epidemiology and integrated control strategies

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Abstract

Bovine Coronavirus (BCoV) is a globally significant pathogen causing respiratory and enteric diseases in cattle, including calf diarrhea, winter dysentery, and contributing to the bovine respiratory disease complex. As a Betacoronavirus closely related to human coronavirus OC43, BCoV poses potential zoonotic risks, highlighting the importance of a One Health approach. The virus exhibits considerable genetic diversity, particularly in the spike protein, influencing virulence and host range. Transmission occurs via fecal-oral, aerosol, and fomite routes, with outbreaks influenced by age, season, and environmental factors. Host defense involves both mucosal and systemic immunity, mediated by antibodies, cytokines, and interferons. Diagnostic methods have advanced from conventional serology and virus isolation to molecular assays, CRISPR-based detection, and metagenomics. Control strategies combine biosecurity, colostrum management, nutrition, herd-level practices, and vaccination, though current vaccines face limitations. Future research should focus on molecular epidemiology, next-generation vaccines, and integration of genomics with field surveillance to enhance outbreak prediction and management.

Keywords: Bovine Coronavirus (BCoV), calf diarrhea, respiratory disease, molecular epidemiology, one health, vaccination strategies, diagnostics and surveillance

1. Introduction

Coronaviruses are a diverse group of enveloped, positive-sense, single-stranded RNA viruses belonging to the family Coronaviridae and order Nidovirales (King *et al.*, 2011; Woo *et al.*, 2012) [17, 37]. Based on phylogenetic and genomic characteristics, they are classified into four genera: Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus, infecting a wide range of hosts including mammals and birds (Woo *et al.*, 2012) [37]. These viruses are associated with a broad spectrum of diseases affecting respiratory, enteric, hepatic, and neurological systems, with varying degrees of severity (Fehr & Perlman, 2015) [11]. Several animal coronaviruses, including avian infectious bronchitis virus (IBV), Porcine Epidemic Diarrhea Virus (PEDV), feline coronavirus (FCoV), and bovine coronavirus (BCoV), are recognized as major pathogens impacting livestock health, productivity, and animal welfare globally (Jackwood, 2012; Jung & Saif, 2015; Pedersen, 2009; Saif, 2010) [15, 16, 26, 30]. The high mutation rates and frequent recombination events characteristic of coronaviruses facilitate viral evolution, enabling host adaptation, interspecies transmission, and the emergence of novel strains with potential zoonotic implications (Woo *et al.*, 2012) [37]. Among these, Bovine Coronavirus (BCoV) is of particular significance in cattle production systems. BCoV, a member of the genus Betacoronavirus (subgenus Embecovirus), is associated with multiple clinical syndromes, including neonatal calf diarrhea, winter dysentery in adult cattle, and respiratory infections contributing to the Bovine Respiratory Disease (BRD) complex (Saif, 2010; Boileau & Kapil, 2010; Vlasova & Saif, 2021) [4, 30, 35]. The virus exhibits pneumoenteric tropism, infecting both the gastrointestinal and respiratory epithelium, which leads to clinical manifestations such as diarrhea, dehydration, reduced growth performance, respiratory distress, and decreased milk production (Vlasova & Saif, 2021) [35].

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These disease conditions contribute to substantial economic losses in both dairy and beef industries.

BCoV infections are often characterized by rapid transmission within herds, facilitated by high levels of viral shedding through feces and respiratory secretions, particularly in young and immunocompromised animals (Saif, 2010; Boileau & Kapil, 2010) [4, 30]. The virus plays a multifactorial role in disease complexes such as BRD, where it interacts with secondary bacterial pathogens, exacerbating clinical severity (Vlasova & Saif, 2021) [35].

Beyond its direct impact on cattle health, BCoV has broader implications for both animal and human health, making it highly relevant within the One Health framework (Fig. 1). Molecular and phylogenetic studies have demonstrated a close genetic relationship between BCoV and human coronavirus OC43 (HCoV-OC43), suggesting a shared evolutionary origin and potential historical interspecies transmission events (Vijgen *et al.*, 2006; Lau *et al.*, 2011) [18, 34]. Furthermore, BCoV-like viruses have been identified in a variety of domestic and wild animal species, including wild

ruminants and other mammals, indicating the ability of these viruses to cross species barriers and circulate across multiple hosts (Lau *et al.*, 2011; Vlasova & Saif, 2021) [18, 35].

This cross-species adaptability highlights the importance of continuous surveillance and molecular characterization of coronaviruses in livestock populations, not only to safeguard animal health but also to mitigate potential public health risks associated with zoonotic transmission (Woo *et al.*, 2012; Lau *et al.*, 2011) [18, 37].

The One Health approach, which integrates human, animal, and environmental health, provides a comprehensive framework for understanding and managing pathogens such as BCoV. Given the demonstrated capacity of coronaviruses to emerge from animal reservoirs and adapt to new hosts, integrated surveillance, interdisciplinary collaboration, and proactive control strategies are essential to prevent future outbreaks and ensure both livestock productivity and global health security (Fehr & Perlman, 2015; Woo *et al.*, 2012) [11, 37].

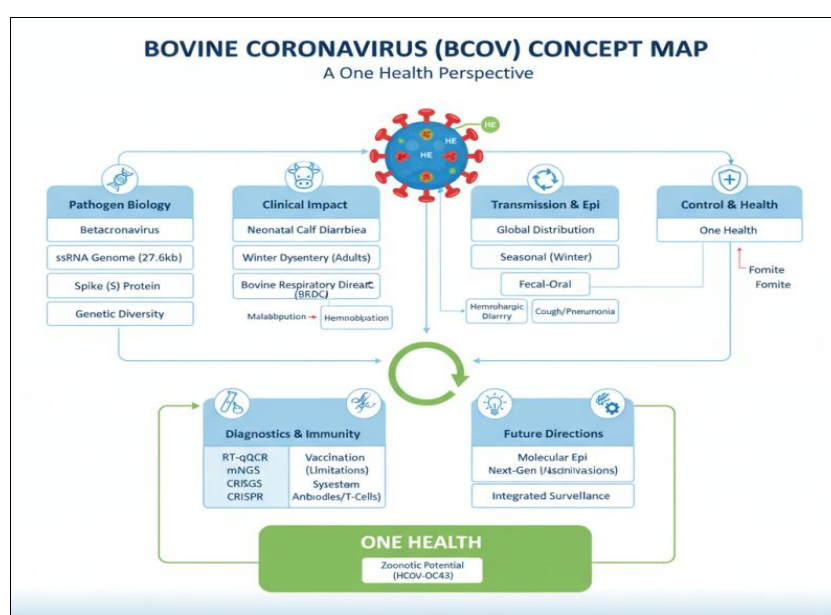


Fig 1: Bovine Coronavirus (BCoV) Concept Map: A One Health Perspective

2. Historical background and taxonomy

The earliest reports of a coronavirus-like agent associated with neonatal calf diarrhea date back to the early 1970s. Using electron microscopy, Stair *et al.* (1972) [32] identified pleomorphic, fringed viral particles in fecal samples from diarrheic calves, consistent with members of the family *Coronaviridae*. Shortly thereafter, Mebus *et al.* (1976) [22] successfully propagated and characterized the virus in experimental calves, demonstrating its pathogenicity and establishing it as a primary etiological agent of neonatal calf diarrhea. These pioneering studies laid the foundation for recognizing bovine coronavirus (BCoV) as a distinct enteric and respiratory pathogen of cattle.

Taxonomically, BCoV is classified within the genus *Betacoronavirus*, subgenus *Embecovirus*, under the family *Coronaviridae* and order *Nidovirales* (King *et al.*, 2011; Woo *et al.*, 2012) [17, 37]. A defining feature of members of the *Embecovirus* subgenus is the presence of the hemagglutinin-esterase (HE) glycoprotein, in addition to the canonical structural proteins spike (S), membrane (M), envelope (E), and nucleocapsid (N) which are conserved across coronaviruses (Woo *et al.*, 2012) [37]. Recent molecular studies further confirm that HE plays a critical role in receptor

binding and viral entry through interaction with sialic acid receptors, highlighting its functional importance in virus biology and evolution (Russell, 2024) [29]. BCoV isolates have been described under multiple strain names, including the well-characterized “Mebus” strain, and exhibit a global distribution in cattle populations (Saif, 2010) [30]. Serological and molecular investigations have consistently demonstrated widespread exposure and frequent detection of BCoV in both enteric and respiratory disease contexts across continents (Boileau & Kapil, 2010; Vlasova & Saif, 2021) [4, 35].

From early virological investigations to contemporary molecular studies, BCoV has been shown to possess a broad tissue tropism, infecting both intestinal and respiratory epithelial cells. This dual tropism underlies its association with multiple clinical syndromes, including neonatal calf diarrhea, winter dysentery in adult cattle, and respiratory disease contributing to the Bovine Respiratory Disease (BRD) complex (Saif, 2010; Vlasova & Saif, 2021) [30, 35]. Recent experimental and genomic investigations further support that BCoV remains a major pneumoenteric pathogen and continues to be widely detected in cattle populations with respiratory and enteric involvement. The virus is efficiently transmitted within herds through fecal and respiratory

shedding, contributing to its epidemiological significance and economic impact on livestock production systems (Boileau & Kapil, 2010) [4].

Advances in molecular phylogenetics have provided important insights into the evolutionary relationships of BCoV within the *Embecovirus* lineage. Comparative genomic analyses have demonstrated that BCoV is closely related to other animal and human coronaviruses, particularly human coronavirus OC43 (HCoV-OC43). Molecular clock studies suggest that HCoV-OC43 likely originated from a bovine-like coronavirus through a relatively recent zoonotic transmission event, possibly occurring in the late 19th century (Vijgen *et al.*, 2006; Lau *et al.*, 2011) [18, 34]. Recent genomic studies further support this close relationship, reporting high sequence homology between bovine and human coronaviruses and reinforcing concerns regarding zoonotic potential.

More recent genomic surveillance has documented both conserved and evolving features within circulating BCoV lineages. While the overall genome organization remains stable and characteristic of *Embecovirus*, ongoing mutations and recombination events particularly in the spike (S) and HE genes contribute to viral evolution, antigenic variation, and potential host adaptation (Vlasova & Saif, 2021; Woo *et al.*, 2012) [35, 37]. Contemporary studies have identified emerging variants with mutations in key functional regions, including the receptor-binding domains of spike and HE proteins, highlighting the dynamic nature of BCoV evolution and the need for continued surveillance. Additionally, recent sequencing efforts have confirmed substantial genetic diversity among circulating strains and emphasized the importance of molecular characterization for understanding disease dynamics and improving control strategies.

In summary, BCoV was first identified in the early 1970s as a coronavirus associated with calf enteritis and was subsequently established as a major pathogen affecting both the enteric and respiratory systems of cattle. As a member of the genus *Betacoronavirus* (subgenus *Embecovirus*), BCoV shares close evolutionary relationships with other animal and human coronaviruses, including HCoV-OC43. The growing body of genomic and epidemiological evidence, including recent studies on viral evolution and host adaptation, underscores the importance of integrating classical virology with modern molecular tools and One Health surveillance approaches to better understand the ecology, evolution, and zoonotic potential of BCoV (Vijgen *et al.*, 2006; Woo *et al.*, 2012) [34, 37].

3. Epidemiology and transmission of bovine coronavirus

3.1 Global distribution

Bovine Coronavirus (BCoV) is a globally distributed pathogen affecting cattle populations across both developed and developing livestock production systems. Numerous epidemiological investigations have demonstrated that BCoV is widely prevalent in both dairy and beef herds, although detection rates vary depending on geographic location, management practices, and diagnostic approaches (Saif, 2010; Boileau & Kapil, 2010) [4, 30].

Recent studies continue to confirm its widespread occurrence. For example, a nationwide survey in Kazakhstan reported the detection of BCoV in cattle populations, highlighting its continued global presence (Perfilyeva *et al.*, 2025) [27]. Similarly, investigations in Korea have demonstrated frequent detection of BCoV in fecal samples from both clinically affected and apparently healthy cattle, suggesting endemic circulation within herds and the potential role of subclinical carriers in disease transmission (Cho *et al.*, 2024) [6].

Molecular epidemiological studies conducted in different regions, including Asia and Europe, further support the widespread distribution and genetic diversity of BCoV strains circulating globally (He *et al.*, 2019; Vlasova & Saif, 2021) [13, 35]. These findings indicate that BCoV remains an important and persistent pathogen in cattle populations worldwide.

3.2 Seasonality and risk factors

BCoV infections exhibit marked seasonal patterns, with increased incidence during colder months, particularly in temperate regions. This seasonal trend is strongly associated with outbreaks of winter dysentery in adult cattle, characterized by acute onset of diarrhea and rapid herd-level spread (Park *et al.*, 2024; Boileau & Kapil, 2010) [4, 25]. Environmental conditions during winter, such as low temperatures, increased humidity, and confinement housing, are conducive to viral survival and transmission.

Several risk factors influence the epidemiology and transmission dynamics of BCoV within herds. These include herd size, age structure of the population, stocking density, ventilation, and overall biosecurity practices (Saif, 2010; Vlasova & Saif, 2021) [30, 35]. Young calves, particularly those with inadequate passive immunity, are highly susceptible to enteric infections, while stress factors such as transportation, weaning, and crowding predispose animals to respiratory disease.

Management-related factors, including poor hygiene, inadequate colostrum intake, and intensive production systems, further enhance viral transmission. Therefore, implementation of robust biosecurity measures, optimization of housing conditions, and reduction of stressors are critical for mitigating the risk and spread of BCoV infections.

3.3 Transmission routes

BCoV is transmitted through multiple routes, facilitating efficient spread within and between cattle populations.

3.3.1 Fecal-Oral transmission

The primary mode of transmission of BCoV is via the fecal-oral route. Infected animals shed large quantities of virus in feces, leading to contamination of the environment, feed, water sources, and housing surfaces (Saif, 2010; Boileau & Kapil, 2010) [4, 30]. Susceptible animals acquire infection through ingestion of contaminated materials, making this route particularly significant in neonatal and pre-weaned calves. Molecular detection studies have consistently identified BCoV RNA in fecal samples of infected animals, confirming the importance of this transmission pathway (Li *et al.*, 2024; Vlasova & Saif, 2021) [19, 35].

3.3.2 Aerosol/Respiratory transmission

Respiratory transmission plays a crucial role in the spread of BCoV, particularly in relation to the Bovine Respiratory Disease (BRD) complex. The virus is shed in nasal secretions and can be transmitted via aerosols and respiratory droplets during close animal contact (Saif, 2010) [30].

Experimental and field studies have demonstrated that calves shedding BCoV through nasal routes are at increased risk of developing respiratory disease, highlighting the importance of airborne transmission in feedlot and intensive production systems (O'Donoghue *et al.*, 2025) [23]. This route is especially relevant under conditions of high stocking density and poor ventilation.

3.3.3 Fomite/Indirect transmission

Indirect transmission through contaminated fomites represents an additional pathway for BCoV spread, particularly in intensive farming environments. Equipment, feeding utensils, bedding materials, clothing, and human handlers can serve as mechanical vectors for virus dissemination (Saif, 2010; Vlasova & Saif, 2021) [30, 35].

BCoV is capable of surviving on surfaces for varying periods under favorable environmental conditions, thereby facilitating indirect transmission between animals and across facilities (Zhu *et al.*, 2022) [40]. Consequently, strict hygiene protocols, regular disinfection of equipment, and controlled farm access are essential components of effective disease prevention strategies.

4. Pathogenesis and Clinical manifestations

4.1 Enteric vs. Respiratory infection mechanisms

Bovine Coronavirus (BCoV) exhibits a characteristic dual tropism, infecting both the gastrointestinal and respiratory systems of cattle. This pneumoenteric nature is central to its pathogenesis and contributes to the diverse clinical manifestations observed across different age groups and production systems (Saif, 2010; Vlasova & Saif, 2021) [30, 35]. The mechanisms of infection in enteric and respiratory tissues, while sharing common viral entry pathways, result in distinct pathological outcomes.

4.2 Enteric infections

In neonatal calves, BCoV primarily targets the epithelial cells lining the small intestine, particularly the villous enterocytes. The virus attaches to host cell receptors, facilitating entry via receptor-mediated endocytosis, followed by replication within the cytoplasm. Viral replication leads to destruction and sloughing of enterocytes, resulting in villous atrophy and disruption of intestinal architecture (Vlasova *et al.*, 2021; Boileau & Kapil, 2010) [4, 35].

The loss of absorptive surface area impairs nutrient and fluid absorption, leading to malabsorption and osmotic diarrhea. Clinically, affected calves exhibit profuse watery diarrhea, dehydration, electrolyte imbalance, and reduced weight gain. In severe cases, especially under conditions of inadequate colostral immunity or concurrent infections, morbidity and mortality may be significant (Saif, 2010; Vlasova & Saif, 2021) [30, 35].

4.3 Respiratory infections

In addition to enteric disease, BCoV infects the respiratory tract, particularly the nasal mucosa, trachea, and bronchi. The virus utilizes similar receptor-mediated mechanisms for entry into respiratory epithelial cells, followed by intracellular replication and localized tissue damage (Saif, 2010; Vlasova & Saif, 2021) [30, 35].

Respiratory infection is associated with clinical signs such as nasal discharge, coughing, fever, and varying degrees of respiratory distress. Importantly, BCoV plays a contributory role in the Bovine Respiratory Disease (BRD) complex, a multifactorial condition involving viral and bacterial pathogens. BCoV infection can alter the integrity of the respiratory epithelium and modulate host immune responses, thereby facilitating colonization by opportunistic bacterial pathogens such as *Mannheimia haemolytica* and *Pasteurella multocida* (Boileau & Kapil, 2010) [4].

Furthermore, studies have indicated that BCoV infection may enhance bacterial adherence to respiratory epithelial cells through upregulation of adhesion molecules, thereby

exacerbating disease severity and promoting secondary infections (Fahkrajang *et al.*, 2021) [10]. This synergistic interaction between viral and bacterial agents significantly contributes to the pathogenesis and economic impact of BRD in cattle populations.

4.4 Clinical syndromes associated with Bovine Coronavirus (BCoV)

Bovine Coronavirus (BCoV) is associated with multiple clinically significant syndromes in cattle, reflecting its dual tropism for enteric and respiratory tissues. These syndromes vary with age, immune status, and management conditions, and collectively contribute to substantial economic losses in cattle production systems (Saif, 2010; Vlasova & Saif, 2021) [30, 35].

4.5 Neonatal calf diarrhea

In neonatal calves, BCoV is a major etiological agent of enteric disease, commonly referred to as neonatal calf diarrhea. The virus infects and destroys villous enterocytes in the small intestine, leading to villous atrophy, impaired nutrient absorption, and osmotic diarrhea (Vlasova *et al.*, 2021; Boileau & Kapil, 2010) [4, 35].

Clinically, affected calves present with profuse watery diarrhea, dehydration, lethargy, reduced suckling reflex, and weight loss. Although the disease is often self-limiting, its severity can increase under conditions of inadequate passive transfer of immunity, poor hygiene, or concurrent infections, resulting in significant morbidity and, in some cases, mortality (Saif, 2010; Vlasova & Saif, 2021) [30, 35].

4.6 Winter dysentery

In adult cattle, BCoV is a well-recognized cause of winter dysentery, a highly contagious disease characterized by sudden onset of diarrhea, which may be hemorrhagic in nature. Outbreaks typically occur during colder months and are often associated with rapid spread within herds (Park *et al.*, 2024; Boileau & Kapil, 2010) [4, 25].

Clinically, affected animals may exhibit diarrhea, decreased feed intake, depression, and a marked drop in milk production, leading to significant economic losses in dairy operations. Although the precise pathogenesis is not fully elucidated, BCoV infection is believed to disrupt intestinal epithelial integrity, resulting in fluid loss, inflammation, and altered gut function (Saif, 2010; Park *et al.*, 2024) [25, 30].

4.7 Bovine Respiratory Disease Complex (BRD Complex)

BCoV is an important viral component of the Bovine Respiratory Disease (BRD) complex, a multifactorial condition involving interactions between viral and bacterial pathogens, host immunity, and environmental stressors. While BCoV infection alone may cause mild to moderate respiratory signs, it frequently acts synergistically with bacterial pathogens such as *Mannheimia haemolytica* and *Pasteurella multocida*, exacerbating disease severity (Saif, 2010; Boileau & Kapil, 2010) [4, 30].

BCoV infection can compromise the integrity of the respiratory epithelium and impair mucociliary clearance, thereby facilitating bacterial colonization and invasion. This interaction enhances disease progression, resulting in clinical manifestations such as coughing, nasal discharge, fever, and pneumonia in severe cases (Fahkrajang *et al.*, 2021; Vlasova & Saif, 2021) [10, 35]. The role of BCoV in BRD highlights its significance not only as a primary pathogen but also as a key contributor to complex respiratory disease dynamics in cattle.

5. Molecular characteristics and Genetic diversity

5.1 Genome structure

Bovine Coronavirus (BCoV) is a member of the genus *Betacoronavirus* within the family *Coronaviridae*. Its genome consists of a single-stranded, positive-sense RNA approximately 27-32 kb in length, consistent with other coronaviruses (Woo *et al.*, 2012) [37]. The genome organization follows the canonical coronavirus structure: 5'-UTR-ORF1a-ORF1b-Spike (S)-Hemagglutinin-Esterase (HE)-Membrane (M)-Envelope (E)-Nucleocapsid (N)-3'-UTR (Cavanagh, 2005) [5].

The ORF1a and ORF1b regions encode non-structural proteins that form the replication-transcription complex, which is essential for viral RNA synthesis and processing. The structural proteins Spike (S), Hemagglutinin-Esterase (HE), Membrane (M), Envelope (E), and Nucleocapsid (N) play critical roles in virion assembly, host interaction, and viral infectivity (Woo *et al.*, 2012; Vlasova & Saif, 2021) [35, 37]. Among these, the spike (S) protein is primarily responsible for mediating viral entry through binding to host cell receptors and initiating membrane fusion (Cavanagh, 2005) [5].

5.2 Spike (S) Protein variations and virulence

The spike (S) glycoprotein of BCoV is a key determinant of host range, tissue tropism, and virulence. Structurally, it is divided into two functional subunits: S1, which mediates receptor binding, and S2, which facilitates membrane fusion. Variations within the S1 subunit, particularly in the Receptor-Binding Domain (RBD), significantly influence viral infectivity and host specificity (Martínez *et al.*, 2012; Vlasova & Saif, 2021) [20, 35].

Genetic mutations and amino acid substitutions in the S protein can alter antigenicity, enabling immune evasion and affecting virus neutralization. Such variations have important

implications for vaccine efficacy and the emergence of new viral variants (Woo *et al.*, 2012) [37]. Recent analyses have identified specific mutations in the S gene associated with altered tissue tropism and increased pathogenicity. For example, certain amino acid substitutions have been linked to enhanced replication in the respiratory tract, contributing to more severe respiratory disease manifestations (Zhao *et al.*, 2025) [39].

These findings highlight the central role of the spike protein in BCoV evolution and pathogenesis, as well as its importance as a primary target for vaccine and therapeutic development.

5.3 Phylogenetic lineages

BCoV exhibits considerable genetic diversity, with circulating strains classified into distinct phylogenetic lineages based on analyses of the S gene, HE gene, and whole-genome sequences. These lineages often reflect geographical distribution, host adaptation, and evolutionary divergence (Lau *et al.*, 2011; Vlasova & Saif, 2021) [18, 35].

Recent molecular epidemiological studies have further elucidated the phylogenetic structure of BCoV. For instance, Li *et al.* (2024) [19] identified multiple clades of BCoV strains circulating in Southwest China, with evidence suggesting potential cross-species transmission between cattle and goats. Such findings reinforce the dynamic nature of BCoV evolution and its capacity for host adaptation.

Phylogenetic analyses are essential for understanding viral evolution, tracking transmission pathways, and identifying emerging variants (Fig. 2). The observed genetic diversity among BCoV strains underscores the importance of continuous molecular surveillance and genomic characterization to support vaccine development and inform effective disease control strategies (Woo *et al.*, 2012; Vlasova & Saif, 2021) [35, 37].

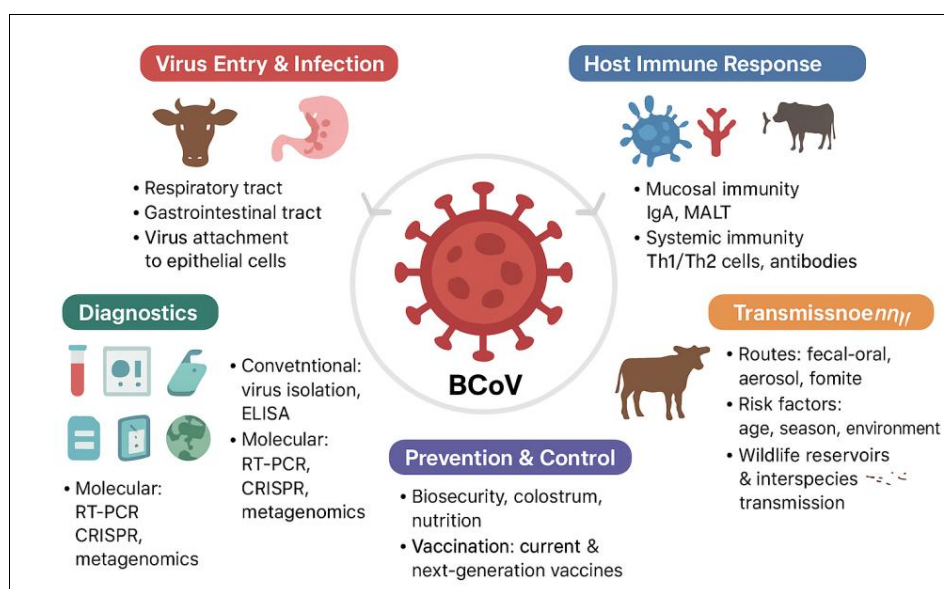


Fig 2: Bovine Coronavirus Dynamics and Management Strategies

6. Host immune response and Immunopathology

6.1 Mucosal and Systemic immunity

Bovine Coronavirus (BCoV) infection induces both mucosal and systemic immune responses, which play a critical role in controlling viral replication and determining clinical outcomes (Saif, 2010) [30]. Given the pneumoenteric nature of BCoV, immune responses are initiated at both gastrointestinal and respiratory mucosal surfaces and subsequently extend to systemic compartments.

6.2 Mucosal immunity

The mucosal immune system constitutes the first line of defense against BCoV infection, as the virus primarily targets epithelial surfaces of the gastrointestinal and respiratory tracts. At these sites, mucosal immune responses are mediated by Mucosal-Associated Lymphoid Tissues (MALT), which facilitate antigen recognition and initiation of localized immune responses (Wagstaffe *et al.*, 2024) [36].

A key component of mucosal immunity is the production of secretory immunoglobulin A (IgA), which plays a crucial role in neutralizing viral particles and preventing their attachment and entry into epithelial cells (Righi, 2023; Vlasova & Saif, 2021) [28, 35]. In neonatal calves, passive transfer of maternal antibodies particularly IgA and IgG through colostrum is essential for early protection against BCoV infection (Saif, 2010) [30]. Insufficient mucosal immunity can lead to increased viral replication and more severe clinical disease.

6.3 Systemic immunity

Following initial mucosal infection, BCoV may induce systemic immune responses characterized by activation of adaptive immune mechanisms. These include the proliferation of T helper (Th) cells, activation of cytotoxic T lymphocytes (CTLs), and production of virus-specific antibodies (Vlasova & Saif, 2021) [35].

The balance between Th1- and Th2-mediated responses is critical in determining disease outcome. Th1 responses are typically associated with cell-mediated immunity and viral clearance, whereas Th2 responses promote humoral immunity. Dysregulation of this balance may influence disease severity and persistence (Holthausen *et al.*, 2026) [14].

6.4 Cytokine and Interferon responses

The innate immune response to BCoV is characterized by rapid induction of cytokines and interferons, which are essential for limiting viral replication and shaping subsequent adaptive immunity (Saif, 2010) [30].

Cytokine Responses

Upon infection, host epithelial and immune cells produce pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), and interleukin-1 β (IL-1 β). These mediators facilitate the recruitment and activation of immune cells at the site of infection, contributing to viral clearance (Holthausen *et al.*, 2026) [14].

However, excessive or prolonged cytokine production can result in tissue damage, inflammation, and exacerbation of clinical disease. Such dysregulated responses may contribute to intestinal damage in enteric infections and lung pathology in respiratory disease (Holthausen *et al.*, 2026; Vlasova & Saif, 2021) [14, 35].

6.5 Interferon responses

Interferons (IFNs) play a central role in antiviral defense against BCoV. Type I interferons (IFN- α and IFN- β) are produced early during infection and induce an antiviral state in neighboring cells by upregulating interferon-stimulated genes. Type III interferons (IFN- λ), which are predominantly expressed at epithelial surfaces, are particularly important in mucosal immunity (Holthausen *et al.*, 2026) [14].

7. Diagnosis and Detection methods

7.1 Conventional and Molecular techniques

Traditional diagnostic approaches for Bovine Coronavirus (BCoV) include virus isolation, electron microscopy, and serological assays. Virus isolation in cell culture remains a definitive method; however, it is labor-intensive, time-consuming, and requires specialized laboratory facilities, limiting its routine application (Saif, 2010) [30].

Electron microscopy enables direct visualization of coronavirus particles based on their characteristic morphology, but its diagnostic utility is constrained by low sensitivity and lack of specificity, particularly in samples with low viral loads (Vlasova & Saif, 2021) [35].

Serological assays, such as Enzyme-Linked Immunosorbent Assays (ELISA), are widely used to detect antibodies against BCoV. These methods are valuable for herd-level surveillance and epidemiological studies; however, they primarily indicate prior exposure rather than active infection (Orozco-Cabrera *et al.*, 2020; Saif, 2010) [24, 30].

7.2 Molecular diagnostic methods

Molecular techniques based on Polymerase Chain Reaction (PCR) have become the gold standard for BCoV detection due to their high sensitivity, specificity, and rapid turnaround time. Reverse transcription PCR (RT-PCR) and quantitative PCR (qPCR) assays enable the detection and quantification of viral RNA in clinical samples such as feces and nasal swabs (Vlasova & Saif, 2021) [35].

Notably, Decaro *et al.* (2008) [8, 9] developed a TaqMan-based real-time qPCR assay for BCoV, demonstrating high analytical sensitivity and specificity, thereby facilitating early diagnosis and differentiation from other enteric and respiratory pathogens. These molecular tools are now routinely used in both diagnostic laboratories and epidemiological investigations.

7.3 Isothermal amplification techniques

Isothermal amplification methods have emerged as rapid and field-deployable alternatives to conventional PCR-based diagnostics. Recombinase Polymerase Amplification (RPA) allows nucleic acid amplification at a constant temperature, eliminating the need for thermal cycling equipment.

Amer (2013) [2] developed a reverse transcription RPA (RT-RPA) assay targeting the nucleocapsid gene of BCoV, providing a sensitive and rapid diagnostic tool suitable for on-site detection. These techniques are particularly valuable in resource-limited settings and for point-of-care diagnostics.

7.4 Emerging metagenomic approaches

metagenomic Next-Generation Sequencing (mNGS) enables unbiased, high-throughput detection of a broad spectrum of pathogens, including BCoV, directly from clinical samples. This approach is especially useful in cases where conventional diagnostics fail to identify the causative agent or in situations involving mixed infections.

Wu *et al.* (2021) [38] demonstrated the application of mNGS in detecting BCoV from nasal exudate samples, highlighting its utility in comprehensive pathogen identification and surveillance of respiratory diseases in cattle.

7.5 Target enrichment metaviromics

To improve the sensitivity and specificity of metagenomic approaches, target enrichment strategies have been developed. These methods selectively capture viral nucleic acids prior to sequencing, thereby increasing the proportion of viral reads and enhancing detection efficiency.

Martínez-Puchol *et al.* (2024) [21] utilized a target enrichment metaviromics approach to investigate coronaviruses in animal-derived samples, demonstrating its effectiveness in detecting BCoV alongside other viral pathogens. Such approaches are increasingly valuable for large-scale surveillance and characterization of viral communities.

7.6 CRISPR/Cas-based detection systems

Recent advancements in molecular diagnostics have led to the development of CRISPR/Cas-based detection platforms for viral pathogens, including BCoV. These systems combine

nucleic acid amplification with CRISPR-mediated detection, offering high sensitivity, specificity, and rapid results.

8. Prevention and Control strategies

8.1 Biosecurity, colostrum management, and nutrition

Effective prevention and control of Bovine Coronavirus (BCoV) require an integrated approach combining biosecurity, immunological protection, and optimized management practices. Implementation of robust biosecurity measures is essential to limit the introduction and spread of BCoV within cattle herds. These measures include restriction of animal movement, control of farm access, sanitation of equipment, and adherence to strict hygiene protocols (Stokstad *et al.*, 2020; Saif, 2010) [30, 33].

Colostrum management plays a critical role in protecting neonatal calves against BCoV infection. Timely ingestion of high-quality colostrum ensures adequate passive transfer of maternal immunoglobulins, particularly IgG and IgA, which provide early protection against enteric and respiratory pathogens (Gorden *et al.*, 2010; Vlasova & Saif, 2021) [12, 35]. Failure of passive transfer significantly increases susceptibility to infection and disease severity.

In addition to passive immunity, proper nutritional management is essential for maintaining immune competence. Balanced diets containing adequate energy, protein, vitamins, and trace minerals support optimal immune function and enhance the animal's ability to respond to infections (O'Donoghue, 2025; Boileau & Kapil, 2010) [4, 23]. Nutritional stress and deficiencies can compromise host defenses, increasing the risk of disease outbreaks.

Vaccination: Current vaccines and limitations

Vaccination is a key component of BCoV control strategies, particularly for reducing the incidence and severity of enteric and respiratory diseases. Commercial vaccines are primarily designed to enhance maternal immunity in pregnant dams, thereby improving passive protection in calves through colostrum (Saif, 2010; Vlasova & Saif, 2021) [30, 35].

Cavirani (2019) [41] emphasized the importance of systematic immunization programs targeting respiratory pathogens to achieve herd immunity and reduce disease burden. However, several limitations affect the efficacy of current vaccines. One major challenge is interference from maternally derived antibodies, which can reduce vaccine-induced immune responses in young calves (O'Donoghue *et al.*, 2025) [23].

Additionally, antigenic variation among circulating BCoV strains, particularly in the Spike (S) protein, may lead to reduced vaccine effectiveness. Variability in management practices, environmental conditions, and herd health status further complicates the optimization of vaccination strategies,

necessitating herd-specific vaccination protocols (Vlasova & Saif, 2021) [35].

Herd-level management practices

Herd-level management practices are critical for minimizing the transmission and impact of BCoV infections. Strategies such as the Sandhills calving system have been shown to reduce pathogen exposure in neonatal calves by segregating age groups and minimizing environmental contamination (O'Donoghue, 2025) [23].

Maintaining optimal housing conditions, including proper ventilation, adequate space, and clean, dry bedding, is essential for reducing environmental stressors and limiting viral transmission (O'Donoghue *et al.*, 2025; Boileau & Kapil, 2010) [4, 23]. Overcrowding and poor ventilation can facilitate the spread of respiratory infections and exacerbate disease severity.

Routine herd health monitoring, early detection of clinical cases, and prompt isolation of infected animals are essential components of effective disease control programs. These measures help to reduce viral shedding and interrupt transmission cycles within the herd (Gorden *et al.*, 2010; Saif, 2010) [12, 30].

9. One health and zoonotic considerations

BCoV and Human coronavirus similarity

Bovine Coronavirus (BCoV) is a member of the Betacoronavirus genus and shares significant genetic and antigenic similarities with human coronavirus OC43 (HCoV-OC43). Studies by Vijgen *et al.* (2006) [34] and Fehr and Perlman (2015) [11] have shown that BCoV and HCoV-OC43 exhibit over 95% nucleotide identity, suggesting a common ancestor and potential for zoonotic transmission (Figure 3). This close relationship has led to hypotheses that BCoV may have been transmitted to humans in the past, possibly contributing to the emergence of HCoV-OC43 as a human pathogen.

Wildlife reservoirs and Interspecies transmission

BCoV primarily infects cattle, but there is evidence of interspecies transmission to other animals, including wildlife. Saif *et al.* (2010) [30] reported that captive wild ruminants could be infected with BCoV, indicating potential wildlife reservoirs. Additionally, studies by Alekseev *et al.* (2008) [1] have demonstrated that BCoV-like viruses can infect gnotobiotic calves, suggesting that BCoV can cross species barriers under certain conditions. These findings underscore the importance of considering wildlife in the epidemiology of BCoV and other coronaviruses (Figure 3).



Fig 3: Integrated Framework for Bovine Coronavirus (BCoV) Management

9. One health and zoonotic considerations (Refined Version)

9.1 BCoV and Human coronavirus similarity

Bovine Coronavirus (BCoV), a member of the genus *Betacoronavirus*, shares significant genetic and antigenic similarities with human coronavirus OC43 (HCoV-OC43). Molecular and phylogenetic analyses have demonstrated a close evolutionary relationship between these viruses, supporting the hypothesis of a shared common ancestor (Vijgen *et al.*, 2006; Woo *et al.*, 2012) ^[34, 37]. Comparative genomic studies indicate a high degree of nucleotide similarity between BCoV and HCoV-OC43, particularly in conserved genomic regions, suggesting the possibility of historical zoonotic transmission events (Vijgen *et al.*, 2006; Fehr & Perlman, 2015) ^[11, 34]. It has been proposed that HCoV-OC43 may have originated from a bovine-like coronavirus through a cross-species transmission event in the relatively recent past, highlighting the zoonotic potential of BCoV and related viruses (Lau *et al.*, 2011) ^[18]. This close genetic relationship underscores the importance of monitoring coronaviruses in livestock populations, as they may serve as reservoirs for the emergence of novel human pathogens.

9.2 Wildlife reservoirs and Interspecies transmission

Although BCoV primarily infects cattle, there is substantial evidence supporting its ability to cross species barriers and infect a range of domestic and wild animals. Studies have reported BCoV or BCoV-like viruses in wild ruminants, indicating the presence of potential wildlife reservoirs that may contribute to virus maintenance and transmission (Saif *et al.*, 2010; Lau *et al.*, 2011) ^[18, 30]. Experimental and field investigations have further demonstrated the capacity of BCoV-like viruses to infect different host species under certain conditions. For instance, Alekseev *et al.* (2008) ^[1] reported that bovine-like coronaviruses could infect gnotobiotic calves, supporting the concept of interspecies transmission and host adaptability. These findings highlight the ecological complexity of BCoV circulation and emphasize the need to consider wildlife-livestock interfaces in epidemiological studies. The ability of BCoV to infect multiple host species reinforces its relevance as a pathogen of concern within the One Health framework.

9.3 Surveillance and One health implications

The One Health approach recognizes the interconnectedness of human, animal, and environmental health and provides a comprehensive framework for addressing emerging infectious diseases. In the context of BCoV, integrated surveillance systems that monitor viral circulation in domestic animals, wildlife, and potentially humans are essential for early detection of emerging strains and prevention of zoonotic spillover events (Vlasova *et al.*, 2021; Woo *et al.*, 2012) ^[35, 37].

Coordinated surveillance programs incorporating molecular diagnostics, genomic sequencing, and epidemiological data can enhance the understanding of viral evolution, transmission dynamics, and cross-species interactions. Such integrated approaches enable timely identification of emerging threats and support the development of targeted intervention strategies. Given the demonstrated evolutionary relationships among coronaviruses and their capacity for interspecies transmission, strengthening One Health-based surveillance and collaboration is critical for mitigating risks to both livestock productivity and public health (Fehr & Perlman, 2015; Lau *et al.*, 2011) ^[11, 18].

10. Future research directions

10.1 Need for Molecular epidemiological studies

Molecular epidemiology is crucial for understanding the transmission dynamics, genetic diversity, and evolution of BCoV. Studies such as those by Liu *et al.* (2006) ^[42] and Zhu *et al.* (2022) ^[40] have provided insights into the prevalence and genetic variability of BCoV in different regions. These studies underscore the necessity for continuous surveillance and molecular characterization to track the emergence of new strains and potential zoonotic transmission. Advancements in next-generation sequencing technologies and bioinformatics tools will further enhance our ability to conduct comprehensive molecular epidemiological studies.

10.2 Development of Next-generation vaccines

The development of effective vaccines against BCoV is imperative to control its impact on cattle health and productivity. Recent research by Sayedahmed *et al.* (2025) ^[43] has explored the use of bovine adenoviral vector-based platforms for vaccine development, offering advantages such as high transduction efficiency and broad tissue tropism. Additionally, in silico approaches by Awadelkareem *et al.* (2024) ^[44] have identified potential multi-epitope vaccine candidates targeting the spike and hemagglutinin-esterase proteins of BCoV. These next-generation vaccine strategies hold promise for providing broader and more durable protection against BCoV infections.

10.3 Integration of genomics and field surveillance

Integrating genomic data with field surveillance is essential for a comprehensive understanding of BCoV epidemiology. Studies by de Mello *et al.* (2024) ^[45] and Li *et al.* (2024) ^[19] have highlighted the importance of whole-genome sequencing in identifying genetic variations and evolutionary patterns of BCoV strains. Combining genomic analyses with real-time field surveillance data can facilitate early detection of outbreaks, monitoring of viral evolution, and assessment of vaccine efficacy. Implementing integrated surveillance systems will enhance our capacity to respond swiftly and effectively to BCoV-related health threats.

Table 1: Key Features and Management Strategies of Bovine Coronavirus (BCoV)

Aspect	Details	References
Virus Type	Enveloped, positive-sense, single-stranded RNA virus; genus Betacoronavirus, subgenus Embecovirus	Woo <i>et al.</i> , 2012 ^[37] ; King <i>et al.</i> , 2011 ^[17]
Genome Structure	~27.6 kb; 5'-UTR-ORF1a-ORF1b-Spike (S)-Hemagglutinin-esterase (HE)-Membrane (M)-Envelope (E)-Nucleocapsid (N)-3'-UTR	Cavanagh, 2005 ^[5]
Key Proteins	Spike (S) - viral entry; HE - receptor binding; M, E, N - virus assembly	Martínez <i>et al.</i> , 2012 ^[20] ; Zhao <i>et al.</i> , 2025 ^[39]
Clinical Syndromes	1. Neonatal Calf Diarrhea (NCD) - diarrhea, dehydration, reduced weight gain2. Winter Dysentery - sudden diarrhea in adults, drop in milk yield3. Bovine Respiratory Disease Complex	Vlasova <i>et al.</i> , 2021 ^[35] ; Park <i>et al.</i> , 2024 ^[25] ;

	(BRDC) - respiratory signs, often with secondary bacterial infections	Fahkrajang <i>et al.</i> , 2021 ^[10]
Transmission Routes	Fecal-oral (ingestion of contaminated feed/water), aerosol/respiratory, fomite/indirect contact	Li <i>et al.</i> , 2024 ^[19] ; Zhu <i>et al.</i> , 2022 ^[40] ; O'Donoghue <i>et al.</i> , 2025 ^[23]
Epidemiology	Global distribution; higher incidence in calves <3 weeks and in colder months (winter dysentery); risk factors: herd size, age, housing density, biosecurity practices	Perfilyeva <i>et al.</i> , 2025 ^[27] ; Cho <i>et al.</i> , 2024 ^[6]
Pathogenesis	Enteric: infects villous enterocytes → villous atrophy → diarrhea, malabsorption Respiratory: infects nasal/tracheal epithelium → cough, nasal discharge; predisposes to secondary bacterial infections	Vlasova <i>et al.</i> , 2021 ^[35] ; Fahkrajang <i>et al.</i> , 2021 ^[10]
Diagnostics	Conventional: virus isolation, EM, ELISA Molecular: RT-PCR, qPCR, RT-RPA Advanced: Metagenomics, target enrichment, CRISPR/Cas detection	Decaro <i>et al.</i> , 2008 ^[8,9] ; Wu <i>et al.</i> , 2021 ^[38]
Control Measures	Biosecurity, hygiene, colostrum management, adequate nutrition, proper housing, vaccination	Gorden <i>et al.</i> , 2010 ^[12] ; Stokstad <i>et al.</i> , 2020 ^[33]
Vaccination Limitations	Maternal antibody interference, variable efficacy, strain-specific responses	O'Donoghue <i>et al.</i> , 2025 ^[23]
Zoonotic Potential	Genetically similar to human coronavirus OC43 (~95% nucleotide identity); possible historical transmission from cattle to humans	Vijgen <i>et al.</i> , 2006 ^[34] ; Fehr & Perlman, 2015 ^[11]

11. Conclusion

Bovine Coronavirus (BCoV) remains a pathogen of considerable significance at the intersection of animal health, livestock productivity, and emerging infectious disease dynamics. Its dual tropism for enteric and respiratory systems, coupled with extensive genetic variability particularly within the spike protein underpins its diverse clinical manifestations and complicates control efforts. Although substantial progress has been made in elucidating its molecular characteristics, epidemiology, and host immune responses, important gaps persist in understanding long-term immunity, viral evolution, and mechanisms governing interspecies transmission.

Advancements in diagnostic technologies, including molecular assays and next-generation sequencing, have greatly enhanced detection and surveillance capabilities. However, effective disease control continues to depend on integrated management strategies encompassing biosecurity, colostrum management, nutritional optimization, herd-level practices, and vaccination. The limitations of current vaccines, particularly in the context of antigenic variation and maternal antibody interference, highlight the urgent need for innovative vaccine platforms capable of providing broader and more durable protection.

Within the One Health framework, the genetic relatedness of BCoV to human coronaviruses and its capacity for cross-species transmission underscore its relevance beyond veterinary medicine. Strengthening integrated surveillance systems that combine genomic, epidemiological, and environmental data will be essential for early detection of emerging variants and mitigation of potential zoonotic risks.

Overall, a multidisciplinary approach integrating molecular epidemiology, advanced diagnostics, vaccine innovation, and One Health-based surveillance is critical for improving the control of BCoV and enhancing preparedness against future coronavirus threats at the human-animal-environment interface.

Conflict of interest

The authors declare that there are no commercial or financial relationships that could be construed as a potential conflict of interest with respect to the research, authorship, and/or publication of this review.

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