Review Article

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Bovine Viral Diarrhea Virus (BVDV) in cattle: Health impacts, reproduction, and management strategies

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ABSTRACT

Bovine Viral Diarrhea Virus (BVDV) is a significant pathogen for the cattle industry worldwide, significantly impacting animal health, reproduction, and economics. This virus belongs to the Pestivirus genus in the *Flaviviridae* family and has a positive-sense, single-stranded RNA genome. BVDV can infect lymphoid cells, hepatocytes, and mucosal epithelium, resulting in systemic disorders, immunosuppression, and the emergence of persistently infected (PI) animals, which serve as the primary reservoir for viral transmission. BVDV infection can be acute or chronic, with clinical symptoms varying depending on the immune status, age, and gestational stage of the animal. Adult cattle tend to experience subclinical infection, while calves are more susceptible to diarrhea, dehydration, thrombocytopenia, and high mortality. In pregnant cows, infection can trigger abortion, the birth of fetuses with congenital defects, or the birth of PI animals. The genetic diversity of BVDV, including non-cytopathic and cytopathic biotypes, as well as BVDV-1, BVDV-2, and HoBi-like (BVDV-3) genotypes, influences virulence, immune response, and vaccination success. Virus transmission occurs horizontally through direct contact, secretions, and contaminated environments, and vertically through transplacental infection. Risk factors include the presence of infected animals, housing density, low biosecurity, and uncontrolled reproductive practices. The economic impact of BVDV is significant, including reduced milk production, beef cattle growth, reproductive efficiency, abortions, and herd control costs. Control strategies emphasize identification and elimination of infected animals, planned vaccination, biosecurity implementation, and sound reproductive management. This review aimed to provide a comprehensive understanding of BVDV, including etiology, pathogenesis, clinical manifestations, risk factors, diagnosis, and control strategies, as a basis for effective herd management and mitigating the economic impact on the cattle industry.

Introduction

Bovine Viral Diarrhea Virus (BVDV) is a major pathogen in the cattle industry, significantly impacting animal health, reproduction, and economics (Khodakaram-Tafti and Farjanikish, 2017). This virus belongs to the Pestivirus genus in the *Flaviviridae* family and has a positive-sense, single-stranded RNA genome capable of infecting various cell types, including lymphoid cells, hepatocytes, and mucosal epithelium (Rana *et al*., 2025a). BVDV infection can be acute or chronic, with persistently infected (PI) animals serving as the primary reservoir that maintains the virus's presence in the livestock population (Givens and Marley, 2013). The virus's ability to induce immunotolerance in fetuses presents a unique challenge in disease control (Smirnova *et al*., 2009).

Since its first recognition in the mid-20th century, BVDV has been known to cause a variety of clinical disorders in cattle (Nugroho *et al*., 2022). In adult animals, acute infection is generally subclinical, although fever, leukopenia, mild diarrhea, and decreased milk production may sometimes occur (Hou *et al*., 2025). Calves and young cattle are more susceptible to severe forms of infection, including severe diarrhea, dehydration, thrombocytopenia, and high mortality (Hessman *et al*., 2012). In pregnant cows, BVDV infection can cause abortion, the birth of fetuses with congenital abnormalities, or the birth of PI animals that appear healthy but serve as a permanent source of infection for the herd (Bachofen *et al*., 2013).

BVDV exhibits extensive genetic diversity, which influences virulence, clinical symptoms, and the immune response of animals (Pang *et al*., 2023). Classically, the virus is classified into two biotypes based on their effects in cell culture: non-cytopathic (ncp) and cytopathic (cp) (Peterhans *et al*., 2010). The ncp biotype is generally associated with subclinical infections and the establishment of PI animals, while the cp biotype is often implicated in mucosal disease in PI animals (Brodersen, 2014). Molecular analysis further subdivides BVDV into BVDV-1, BVDV-2, and HoBi-like pestivirus (BVDV-3), each with distinct subgenotypes with distinct regional distribution patterns and epidemiological impacts, thus influencing vaccination approaches and control strategies (Rana *et al*., 2025b).

BVDV transmission can occur through both horizontal and vertical routes. Horizontal transmission involves direct contact between animals, mucosal secretions, urine, feces, and contamination of equipment or the environment (Robi *et al*., 2024). Meanwhile, vertical transmission occurs when pregnant cows become infected, which can result in abortion, birth defects, or the birth of PI animals (Fray *et al*., 2000). Risk factors include the presence of PI animals, livestock density, uncontrolled reproductive practices, poor biosecurity, and interactions with wild ruminants or other livestock groups (Rana *et al*., 2025b). Understanding these transmission routes and risk factors is crucial for designing effective control strategies.

The economic impact of BVDV is significant. Infection with this virus causes decreased milk production, growth in beef cattle, and reproductive efficiency within herds (Houe, 2003). Abortions, births with abnormalities, and mortality cause direct losses, while the costs of vaccination, control of PI animals, and biosecurity measures add to the indirect losses (Yarnall and Thrusfield, 2017). Various global studies estimate that losses from BVDV can reach tens to hundreds of millions of US dollars annually,

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depending on the prevalence and population size of the livestock in a given region (Pinior *et al*., 2019).

This study aimed to provide a comprehensive overview of BVDV, covering etiology, pathogenesis, clinical symptoms, risk factors, diagnostic methods, and control strategies. This information is expected to provide a basis for implementing effective herd management programs, infection prevention efforts, and mitigating the economic impact on the cattle farming sector.

History

Bovine Viral Diarrhea (BVD) was first identified as a new disease of cattle in 1946, when veterinarians from the New York State Veterinary College reported nonspecific gastrointestinal, mucosal, and reproductive disorders in several herds in New York, USA (Newcomer, 2021). Subsequent research demonstrated that the condition was caused by an infectious agent that could be transmitted experimentally through inoculation of feces and blood from diseased animals, confirming that the disease was a new entity distinct from rinderpest or other domestic animal diseases known at the time (Fulton, 2009).

The formal isolation and identification of the causative agent as a virus did not occur until 1957, when the virus, later named BVDV, was successfully obtained and virologically analyzed (Goens, 2002). This isolation process allowed for further study of the virus's biological characteristics, including its genomic structure and antigenic properties, and distinguished BVDV from other previously known viruses (Abe *et al*., 2016).

In the following decade, research on BVDV revealed that the virus is divided into two biotypes based on its effects on cell cultures: non-cytopathic (ncp) and cytopathic (cp) (Chi *et al*., 2022). The distinction between these two biotypes is key to understanding pathogenesis, particularly regarding the establishment of PI animals and the development of mucosal disease (Ammari *et al*., 2010). These findings further elucidate the mechanism of BVDV infection and its importance for developing disease control strategies (Bielefeldt-Ohmann, 2020).

The development of molecular technology in the late 20th and early 21st centuries enabled genome sequencing and genetic analysis of BVDV (Schweizer *et al*., 2021). These findings revealed several genotypes, primarily BVDV-1 and BVDV-2, along with various subgenotypes that have different epidemiological and vaccinological implications in different regions of the world (Khan *et al*., 2024).

Etiology

BVDV is a single-stranded, positive-stranded RNA virus belonging to the Pestivirus genus and the *Flaviviridae* family (Retno *et al*., 2022). This enveloped virus has a genome approximately 12.3 kb long, structured within a single open reading frame (ORF) (Yu *et al*., 1999). This ORF is translated into a polyprotein, which is then processed by viral and host cell proteases into structural and non-structural proteins, which play a crucial role in the virus's ability to infect, replicate, and interact with the host immune system (Wu *et al*., 2023).

The structural proteins of BVDV include the capsid (C) protein and the envelope glycoproteins Erns, E1, and E2 (Qi *et al*., 2022). Among these proteins, E2 acts as the primary antigen, is essential for viral attachment to host cells and is the primary target of the humoral immune response (Al-Kubati *et al*., 2021). Meanwhile, non-structural proteins, such as Npro, p7, NS2/3, NS4A, NS4B, NS5A, and NS5B, function in viral genome replication, viral particle maturation, and modulation of the host immune response (Chi *et al*., 2022).

Based on its genetic and antigenic properties, BVDV is divided into three main species: BVDV-1 (Pestivirus A), BVDV-2 (Pestivirus B), and HoBi-like pestivirus (Pestivirus H). BVDV-1 and BVDV-2 are the most common species worldwide and exhibit high genetic diversity with various subgenotypes (Maya *et al*., 2025). These genetic differences influence virulence levels, clinical symptoms, and the effectiveness of vaccines used in disease control strategies (Zhang *et al*., 2025).

In addition to genetic classification, BVDV is also classified into cytopathic (cp) and non-cytopathic (ncp) biotypes based on their effects on cell culture (Abe *et al*., 2016). The ncp biotype is the most common form found in nature and plays a key role in the establishment of persistent infection when the fetus is infected early in pregnancy (Holthausen *et al*., 2025). In contrast, the cp biotype typically arises through mutation or recombination of the genome of the ncp strain and is closely associated with the development of mucosal disease in persistently infected animals (Tzeng *et al*., 2025).

Molecularly, BVDV exhibits a relatively high mutation rate because its RNA-dependent RNA polymerase (NS5B) enzyme lacks a proofreading mechanism (Zhong *et al*., 1998). This allows the virus to evolve rapidly, evading host immune responses and adapting to selective pressures, including vaccination (Lai *et al*., 1999). Furthermore, BVDV possesses unique immunosuppressive strategies, one of which is through the Npro protein, which suppresses type I interferon production, prolonging the duration of infection and increasing the risk of secondary infections (Hu *et al*., 2026).

Epidemiology

BVDV has a widespread distribution and has been reported in almost all regions with large domestic cattle populations (Melkamsew *et al*., 2025a). Global virus distribution is strongly influenced by cattle production systems, interregional livestock movement, and differences in the implementation of control and biosecurity programs in each country (Richter *et al*., 2019). The prevalence of BVDV infection varies significantly between countries and regions, both in terms of active infection and serological exposure (Su *et al*., 2023). Table 1 summarizes the global epidemiological distribution of BVDV across major geographic regions.

In Europe, BVDV has become a major focus of control and eradication programs in several countries, including Scandinavia, Germany, Switzerland, and Austria (Hult and Lindberg, 2005; Rossmanith *et al*., 2005; Schweizer *et al*., 2021; Wernike *et al*., 2025). These countries reported significant reductions in prevalence after implementing programs that emphasized the identification and elimination of PI animals and livestock movement restrictions (Greiser-Wilke *et al*., 2003). However, in Eastern Europe and several countries with less than optimal control systems, BVDV remains endemic with relatively high prevalence rates (Puspitarani *et al*., 2022).

In North America, BVDV remains a significant health problem in livestock, particularly in intensive livestock systems (Khodakaram-Tafti and Farjanikish, 2017). The United States and Canada report various subgenotypes of BVDV-1 and BVDV-2, with prevalence rates influenced by vaccination practices, stocking density, and farm management (Morin *et al*., 2026; Walz *et al*., 2020). Despite widespread vaccination, PI animals remain a major reservoir for maintaining the virus in the population (Hu *et al*., 2026).

In Latin America, BVDV is highly endemic, particularly in countries with developing beef and dairy cattle production systems (Barragán *et al*., 2025). Seroepidemiological studies in Brazil, Argentina, and Mexico have shown high seroprevalence, indicating widespread and ongoing exposure to the virus (Gomez-Romero *et al*., 2021; Marian *et al*., 2024; Sosa *et al*., 2025). Limited national control programs and high livestock mobility are key factors maintaining virus circulation in the region (Zirra-Shallangwa *et al*., 2022).

In Asia, the distribution of BVDV is uneven and influenced by differences in livestock systems, levels of disease surveillance, and diagnostic capacity (Bashenova *et al*., 2025). The virus has been reported in East Asia, South Asia, Southeast Asia, and West Asia, with BVDV-1 being the most prevalent, with sporadic reports of BVDV-2 and HoBi-like pestivirus (Al-Mubarak *et al*., 2023; Kampa *et al*., 2004; Shah *et al*., 2022; Sudharshana

Table 1. Global distribution and epidemiological characteristics of BVDV across major geographic regions

Region	Epidemiological status	Dominant subgenotypes	Main factors influencing prevalence	Notes	References
Europe	Low prevalence in countries with eradication programs; endemic in parts of Eastern Europe	Mainly BVDV-1 (various subgenotypes) with occasional BVDV-2	National eradication programs, identification and removal of persistently infected (PI) animals, livestock movement restrictions, biosecurity measures	Scandinavia, Germany, Switzerland, and Austria reported significant reductions in prevalence following systematic eradication programs	(Hult and Lindberg, 2005; Rossmanith *et al*., 2005; Greiser-Wilke *et al*., 2003; Schweizer *et al*., 2021; Puspitarani *et al*., 2022; Wernike *et al*., 2025)
North America	Endemic with moderate prevalence	BVDV-1 and BVDV-2	Vaccination programs, intensive cattle production systems, stocking density, farm management practices	United States and Canada report multiple circulating subgenotypes; PI animals remain major reservoirs despite vaccination	(Khodakaram-Tafti and Farjanikish, 2017; Walz *et al*., 2020; Morin *et al*., 2026; Hu *et al*., 2026)
Latin America	Highly endemic	Predominantly BVDV-1 with occasional BVDV-2	Limited national control programs, high livestock mobility, expanding beef and dairy industries	High seroprevalence reported in Brazil, Argentina, and Mexico, indicating widespread viral exposure	(Gomez-Romero *et al*., 2021; Zirra-Shallangwa *et al*., 2022; Marian *et al*., 2024; Barragán *et al*., 2025; Sosa *et al*., 2025)
Asia	Uneven distribution; endemic in several countries	Predominantly BVDV-1; sporadic BVDV-2 and HoBi-like pestivirus	Differences in livestock production systems, surveillance capacity, and diagnostic infrastructure	True prevalence may be underestimated due to limited surveillance and reporting systems in some developing countries	(Sudharshana *et al*., 1999; Kampa *et al*., 2004; Scharnböck *et al*., 2018; Shah *et al*., 2022; Al-Mubarak *et al*., 2023; Bashenova *et al*., 2025)
Africa and Middle East	Limited epidemiological data but evidence of widespread exposure	Mostly BVDV-1 with limited genotype data	Extensive livestock systems, lack of structured control programs, interspecies interactions	Virus reported in domestic cattle and other ruminants; serological studies suggest widespread exposure	(Lysholm *et al*., 2019; Su *et al*., 2023; Ghenoumat *et al*., 2025)

et al., 1999). In many developing countries, limitations in surveillance and reporting likely under-detect the true prevalence of BVDV (Scharnböck *et al.*, 2018).

In Africa and the Middle East, BVDV has been reported in domestic cattle and several other ruminant species (Lysholm *et al.*, 2019). Although epidemiological data in these regions are limited, serological studies indicate widespread exposure to the virus, particularly in extensive livestock systems (Ghenoumat *et al.*, 2025). The lack of structured control programs and high levels of interspecies interaction are thought to contribute to maintaining virus circulation in these areas (Su *et al.*, 2023).

Globally, the spread of BVDV is influenced by a combination of viral biology and human factors, such as cross-border livestock trade, livestock management practices, and animal health policies (Rana *et al.*, 2025b). Differences in control strategies across countries contribute to variations in the epidemiological status of BVDV, emphasizing the importance of an integrated control approach tailored to regional conditions (Hu *et al.*, 2026).

Pathogenesis

BVDV causes disease through a complex interaction with the host's immune system (Melkamsew *et al.*, 2025b). Infection can be acute or persistent, depending on the viral biotype, the host's immune status, and the age or gestational stage at the time of exposure (Kelling and Topliff, 2013). The virus infects various cell types, including lymphocytes, monocytes, epithelial cells, and hepatocytes, resulting in widespread systemic effects (Brodersen, 2014).

In acute infection, non-cytopathic (ncp) BVDV enters epithelial and immune cells through specific receptors and then replicates rapidly (Chase *et al.*, 2004). The virus inhibits type I interferon activation through the Npro and Erns proteins, resulting in transient immunosuppression (Darweesh *et al.*, 2018). This condition makes infected animals more susceptible to secondary infections by other bacterial or viral pathogens (Al-Kubati *et al.*, 2021). Furthermore, the developed humoral and cellular immune responses limit the spread of the virus, so most adult cattle exhibit only subclinical infection or mild symptoms, such as fever, diarrhea, and transient leukopenia (Khodakaram-Tafti and Farjanikish, 2017).

Persistent infection occurs when a fetus is exposed to BVDV ncp during the first trimester of pregnancy (Xue *et al.*, 2009). The virus attacks the developing immune system, resulting in animals being born PI, unable to mount an effective immune response to BVDV (Chase *et al.*, 2004). These PI animals serve as the primary reservoir for virus spread within the population, as they continually shed the virus in saliva, urine, and genital secretions without showing any obvious clinical symptoms (Passler *et al.*, 2016).

Mucosal disease occurs in PI animals after reinfection with the antigenically similar cytopathic (cp) biotype (Bruschke *et al.*, 1998). This cp biotype arises from mutation or genomic recombination of the ncp strain and causes extensive damage to mucosal epithelium, including in the mouth, gastrointestinal tract, and skin (Khodakaram-Tafti and Farjanikish, 2017). These lesions are accompanied by epithelial cell necrosis, severe diarrhea, and severe immunosuppression, often resulting in death (Abdelsalam *et al.*, 2020).

Molecularly, BVDV pathogenesis is influenced by the non-structural proteins NS2/3, which play a role in regulating viral replication and cell apoptosis, and the Npro protein, which suppresses the interferon pathway (Al-Kubati *et al.*, 2021). The combination of immunosuppression, effective viral replication, and epithelial cell damage are key factors determining the variety of clinical symptoms, ranging from subclinical infection to fatal mucosal disease (Hou *et al.*, 2025). Furthermore, the diversity of viral genotypes and biotypes influences virulence, the ability to induce persistent infection, and the response to vaccines, posing challenges in disease control (Walz *et al.*, 2020).

Immune response

The immune response to BVDV involves a complex interplay between the innate and adaptive immune systems, influencing the course of infection and the establishment of PI animals (Chase *et al.*, 2004). Early in the infection, BVDV ncp invades epithelial cells, lymphocytes, and monocytes, triggering the activation of the innate immune response (Pang *et al.*, 2023). The virus inhibits type I interferon production through the Npro and Erns proteins, thereby suppressing the host's antiviral pathway and supporting viral replication (Wang *et al.*, 2024). Furthermore, BVDV can

induce lymphocyte apoptosis, leading to transient leukopenia that weakens the host's ability to fight secondary infections (Wang *et al*., 2021).

The adaptive immune response is characterized by the production of specific antibodies against viral envelope proteins, particularly the E2 glycoprotein, which is the primary antigen for BVDV neutralization (Grigera *et al*., 2000). Furthermore, activation of $CD4^+$ and $CD8^+$ T cells plays a crucial role in destroying infected cells (Collen and Morrison, 2000). In acute infections, the interaction between neutralizing antibodies and cytotoxic T cells is generally effective in controlling the virus, resulting in most animals experiencing subclinical infection or mild symptoms (Taberner *et al*., 2024).

In fetuses infected in the first trimester, BVDV ncp can attack the developing immune system, preventing the fetus from recognizing the virus as a foreign antigen (Morarie-Kane *et al*., 2018). Consequently, the animals are born PI, tolerant to BVDV and continually excrete the virus without mounting an effective immune response (Peterhans and Schweizer, 2013). This tolerance mechanism suggests that the timing of the virus's exposure to the fetal immune system significantly determines the animal's immunological status after birth (Hu *et al*., 2026).

BVDV also suppresses the humoral immune response by reducing antibody production and inhibiting B cell maturation (Al-Kubati *et al*., 2021). Furthermore, the virus modulates cellular responses through the non-structural proteins NS2/3 and NS5A, which suppress T cell activation and proinflammatory cytokine production (Fan *et al*., 2022). These combined immunosuppressive effects increase susceptibility to secondary infections and prolong the period of viral shedding in both PI and acutely infected animals (Melkamsew *et al*., 2025b).

Pathology

The pathology of BVDV reflects tissue damage resulting from viral replication, immunosuppression, and the host's inflammatory response (Bielefeldt-Ohmann, 1995). The most prominent lesions occur in the lymphohematopoietic system, gastrointestinal epithelium, liver, and reproductive organs, with severity varying depending on the viral biotype, host immune status, and animal age (Khodakaram-Tafti and Farjanikish, 2017).

In acute infection, animals experience degeneration and a decrease in the number of lymphocytes in the lymph nodes and spleen, which contribute to leukopenia and transient immune disorders (Han *et al*., 2016). In gastrointestinal tissue, BVDV can cause intestinal villous atrophy, glandular hyperplasia, and mononuclear cell infiltration, which are associated with diarrhea and malabsorption (Van Metre *et al*., 2008). The liver shows hepatocyte degeneration and mononuclear lymphocyte infiltration, although clinical liver changes are generally mild in cases of subclinical infection (Risalde *et al*., 2011).

Infection of fetuses or PI animals results in chronic and systemic lesions (Workman *et al*., 2017). In fetuses infected during the first trimester, BVDV can disrupt organogenesis, causing abortion or congenital abnormalities such as microphthalmia, cerebellar hypoplasia, and skeletal deformities (Stephenson *et al*., 2017). In PI animals, histopathology reveals persistent lymphoid tissue atrophy and mild mononuclear infiltration in epithelial organs (Shin and Acland, 2001).

Mucosal disease, which develops in PI animals after reinfection with the cytopathic biotype, is characterized by extensive damage to the mucosal epithelium (Melkamsew *et al*., 2025b). Histopathological examination reveals multifocal necrosis of the gastrointestinal epithelium, ulceration in the mouth and rumen, and inflammatory mononuclear cell infiltration (Ohmann, 1983). This severe epithelial damage leads to bloody diarrhea, malnutrition, and immunosuppression, ultimately leading to death (Bielefeldt-Ohmann, 1995).

Microscopically, BVDV causes degenerative, inflammatory, and apoptotic changes in various tissues, with distinct patterns between acute and chronic infections and mucosal disease (Hilbe *et al*., 2013). These differences reflect the relationship between viral biotype, host immune status, and pathogenesis pathways, which influence clinical manifestations and disease prognosis (Roshanzamir *et al*., 2025). A thorough understanding of BVDV pathology is essential for histopathological diagnosis, identification of infected animals, and formulation of effective disease control strategies.

Clinical manifestations

BVDV causes a wide range of clinical manifestations, ranging from subclinical infection to severe, potentially fatal disease (Hou *et al*., 2025). The severity and clinical symptoms are influenced by the virus biotype (cytopathic or non-cytopathic), the host's immune status, the age, and the gestational stage of the infected cow (Ullah *et al*., 2025). Table 2 summarizes the range of clinical manifestations associated with BVDV infection in cattle, highlighting differences based on host age, immune status, and gestational stage.

In immunocompetent adult cattle, acute infection with non-cytopathic BVDV is generally subclinical or causes mild symptoms (Walz *et al*., 2010). Clinical signs may include fever, anorexia, depression, and transient leukopenia. Some animals may also experience mild diarrhea, mucosal hyperemia, and a temporary decrease in milk production, which usually resolves within 1–2 weeks (Weerasekara *et al*., 2025). Figure 1 illustrates the broad spectrum of clinical manifestations of BVDV in cattle, ranging from subclinical infection in immunocompetent adult animals, severe systemic disease in calves, reproductive disorders in pregnant heifers, to fatal mucosal disease in PI animals.

Table 2. Spectrum of clinical manifestations of BVDV infection in cattle based on age, immune status, and gestational stage

Cattle group / condition	Type of infection or situation	Major clinical manifestations	Additional characteristics / outcomes
Immunocompetent adult cattle	Acute infection with non-cytopathic (NCP) BVDV	Mild fever, anorexia, depression, transient leukopenia, mild diarrhea, and mucosal hyperemia	Usually subclinical or mild disease; temporary reduction in milk production; recovery generally occurs within 1–2 weeks
Calves or naïve young cattle	Acute infection in immunologically susceptible animals	Severe diarrhea, dehydration, thrombocytopenia, fever, and depression	Higher risk of secondary infections; may cause growth retardation and increased mortality
Pregnant cows (early gestation / first trimester)	Maternal infection during early pregnancy	Abortion, embryonic resorption, and fetal death	Congenital abnormalities may occur, including microphthalmia, cerebellar hypoplasia, and skeletal deformities
Pregnant cows (mid to late gestation)	Fetal infection during immune tolerance period	Birth of persistently infected (PI) calves	Calves may appear clinically normal at birth but shed virus continuously and act as reservoirs
Persistently infected (PI) cattle	Superinfection with cytopathic (CP) BVDV (mucosal disease)	Oral and ruminal ulceration, bloody diarrhea, severe dehydration, anorexia, and drastic weight loss	Severe systemic mucosal lesions; high mortality and rapid clinical deterioration
Various cattle populations	Systemic effects of BVDV infection	Immunosuppression, hematologic disorders, and increased susceptibility to secondary infections	Predisposes animals to bacterial and viral co-infections and worsens overall disease outcome

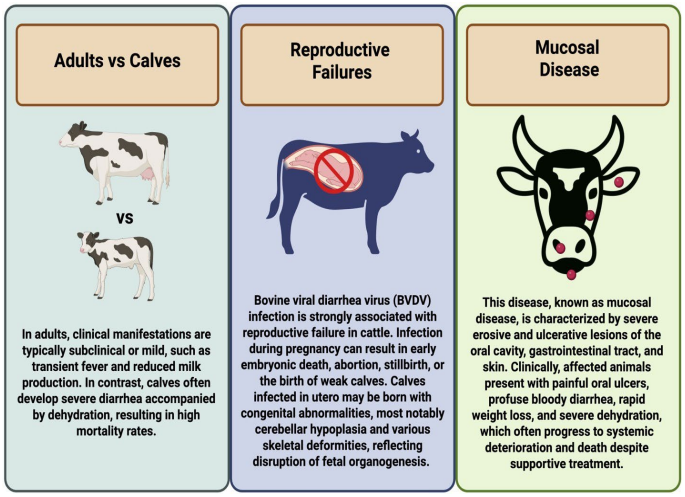

Figure 1. Clinical manifestations.

Infections in calves or animals previously unexposed to BVDV tend to be more severe (Handel *et al*., 2011). Calves often experience severe diarrhea, dehydration, thrombocytopenia, and secondary infections, which worsen the prognosis (Goens, 2002). Furthermore, infection can stunt growth and increase mortality in susceptible populations (Tura *et al*., 2025).

In pregnant cows, BVDV infection can cause serious reproductive problems (Bulcha *et al*., 2025). Exposure to the virus in the first trimester of pregnancy can cause abortion, embryo resorption, or the birth of fetuses with congenital defects, such as microphthalmia, cerebellar hypoplasia, and skeletal deformities (Spetter *et al*., 2020). Meanwhile, infection in the middle to late trimesters can result in PI animals, which appear normal at birth but serve as lifelong reservoirs of the virus (Iotti *et al*., 2019).

Mucosal disease, which occurs in PI animals after reinfection with the cytopathic biotype, is characterized by severe and characteristic clinical symptoms (Peterhans *et al*., 2010). Visible signs include oral and rumen ulceration, bloody diarrhea, severe dehydration, anorexia, drastic weight loss, and death (Cho *et al*., 2023). These lesions reflect systemic damage to the mucosal epithelium and profound immunosuppression (Hu *et al*., 2026).

In addition to classic symptoms, BVDV can also cause nonspecific systemic manifestations, such as immunosuppression, hematologic disorders, and increased susceptibility to secondary infections (Abdelsalam *et al*., 2020). This clinical variation emphasizes the importance of using a combination of clinical assessment, serology, and molecular diagnostics to ensure an accurate diagnosis and identify PI animals in the population (Werid *et al*., 2023).

Diagnosis

Diagnosis of BVDV requires an integrated approach that combines clinical evaluation, serological methods, and virus detection techniques to confirm active infection, identify PI animals, and differentiate between viral biotypes and genotypes (Wang and Pang, 2024). Clinical assessment is usually the initial step, especially during outbreaks, with attention to symptoms such as fever, diarrhea, leukopenia, oral mucosal lesions, and reproductive disorders (Hou *et al*., 2025). However, because many animals are subclinically infected, diagnosis based solely on clinical signs is insufficient to detect PI animals (Ghenoumat *et al*., 2025).

Serological methods are used to detect antibodies to BVDV and assess previous exposure, including response to vaccination (Sozzi *et al*., 2020). Tests such as enzyme-linked immunosorbent assay (ELISA) allow rapid screening of herds, while the virus neutralization test (VNT) is the gold standard for identifying specific neutralizing antibodies (Mahmoodi *et al*., 2015). Limitations of serology include the inability to distinguish between natural infection and vaccination and the failure to detect PI animals that have developed immune tolerance to the virus (Walz *et al*., 2020).

Direct virus detection provides evidence of active infection and is a crucial step in identifying PI animals (Seid *et al*., 2026). Molecular techniques, such as reverse transcription polymerase chain reaction (RT-PCR), allow sensitive and specific detection of viral RNA using blood samples, secretions, or fetal tissue (Dehkordi, 2011). Meanwhile, antigen capture ELISA (ACE) detects viral proteins in serum or leukocytes and is often used for screening livestock populations (Suryohastari *et al*., 2025). Virus isolation via cell culture remains a valid method for biotype confirmation, although it is laboratory-intensive and time-consuming (Rana *et al*., 2025b).

In cases of mucosal disease or abortion caused by BVDV, histopathology and immunohistochemistry can confirm the diagnosis by demonstrating the distribution of the virus and tissue lesions (Fulton, 2009). These methods allow visualization of viral proteins in epithelial or lymphoid cells, thus supporting pathological assessment and confirmation in complex cases (Baszler *et al*., 1995).

Differential diagnosis

The clinical manifestations of BVDV are often nonspecific, so differential diagnosis is essential to distinguish BVDV from other diseases with similar symptoms (Baker, 1995). In cattle, the diarrhea, fever, mucosal lesions, and reproductive disorders caused by BVDV can mimic other gastrointestinal or systemic infections (Tao *et al*., 2013). Diseases such as salmonellosis, paratuberculosis, rotavirus or coronavirus infections, and leptospirosis should be considered because their symptoms can overlap with BVDV infection (Primawidyawan *et al*., 2023).

Reproductive disorders caused by BVDV, such as abortion or the birth of a fetus with congenital abnormalities, must be differentiated from other viral infections, including Akabane, Schmallenberg, or Blue Tongue virus (Agerholm *et al*., 2015). Differences in histopathological lesions and the distribution of affected organs can help determine the etiology (Bianchi *et al*., 2019). Furthermore, mucosal disease caused by BVDV must be differentiated from epizootic foot-and-mouth disease (FMD) and vesicular stomatitis, as both diseases also cause oral ulceration and mucosal changes (Clemmons *et al*., 2021).

Leukopenia and thrombocytopenia caused by BVDV can mimic other hematologic disorders, including bovine herpesvirus-1 (IBR) infection or bacterial septicemia (Chantillon *et al*., 2022). Therefore, the use of laboratory diagnostics, such as serology, RT-PCR, antigen capture ELISA, or virus isolation, is crucial to ensure an accurate diagnosis (Wang *et al*., 2024). The combination of clinical findings, epidemiological data, and laboratory results helps identify BVDV and supports the adoption of appropriate control measures (Walz *et al*., 2020).

Transmission

BVDV is spread through various mechanisms, demonstrating the virus's ability to persist and spread within cattle populations (Khodakaram-Tafti and Farjanikish, 2017). Transmission can occur both horizontally and vertically, with PI animals serving as the primary reservoir (Hu *et al*., 2026). PI animals continuously shed the virus through saliva, urine, genital secretions, and feces, thus serving as a source of infection for other animals in the herd, either through direct contact or indirectly through contaminated equipment, feed, and the environment (Nelson *et al*., 2016). Table 3 summarizes the principal mechanisms of BVDV transmission within cattle populations.

Horizontal transmission of BVDV can occur through close contact between animals, aerosolization of respiratory secretions, and through reproductive fluids during mating or artificial insemination (Fulton, 2009). Infection can also occur iatrogenically, for example, through the use of unsterile syringes or other invasive equipment (Houe, 1995). The rate of

Table 3. Major transmission routes of BVDV in cattle populations.

Transmission route	Source of virus	Mode of transmission	Epidemiological significance
Horizontal transmission	Persistently infected (PI) cattle or acutely infected animals	Direct contact with infected animals, aerosolized respiratory secretions, saliva, urine, feces, and genital secretions	Main mechanism of virus spread within herds; PI animals continuously shed virus and serve as the primary infection source
Vertical transmission	Infected pregnant cows	Transplacental infection of the fetus during early or mid-gestation	May lead to abortion, congenital defects, fetal death, or birth of persistently infected (PI) calves that maintain viral circulation in the herd
Reproductive transmission	Infected bulls or contaminated reproductive materials	Transmission through natural mating or artificial insemination using contaminated semen or reproductive fluids	Facilitates spread between herds and contributes to infection of pregnant cows
Iatrogenic transmission	Contaminated veterinary equipment or biological products	Use of unsterile needles, syringes, surgical instruments, or contaminated vaccines and biological materials	Can introduce the virus into naïve herds if proper hygiene and biosecurity measures are not implemented
Environmental contamination	Virus shed from PI or infected animals	Indirect transmission through contaminated feed, water, equipment, housing surfaces, or farm personnel	Supports indirect spread of the virus within farms, especially under poor biosecurity and high stocking density
Cross-species reservoir transmission	Wild ruminants or other susceptible species	Contact between domestic cattle and wildlife reservoirs or shared grazing environments	Potential auxiliary reservoir that may contribute to viral persistence, although epidemiological impact is generally limited

virus spread within a population is influenced by livestock density, housing management, and biosecurity practices (Werid *et al.*, 2023). Figure 2 illustrates the complex transmission pathways of BVDV in cattle populations, emphasizing the central role of PI animals as the primary reservoir and source of ongoing virus excretion.

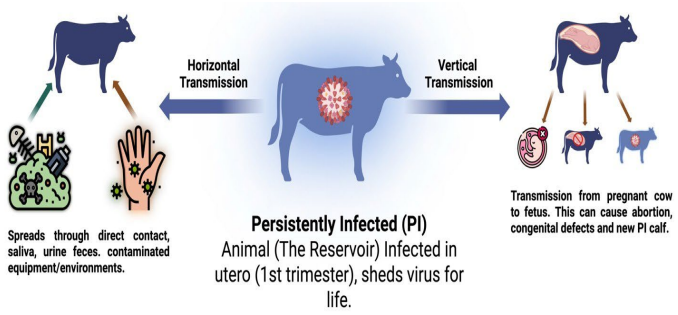

Figure 2. The "Silent Threat" - Transmission and PI animals

Vertical transmission occurs when pregnant cows become infected with BVDV during early or mid-gestation (Tsuboi *et al.*, 2011). The virus crosses the placenta and infects the fetus, which can lead to abortion, the birth of fetuses with congenital defects, or the birth of PI animals that are tolerant to the virus (Brownlie *et al.*, 1987). Persistently infected fetuses then become the primary source of horizontal transmission to subsequent generations, reinforcing the cycle of viral endemicity within the herd (Hamers *et al.*, 1998).

In addition to domestic cattle, several studies suggest that wild ruminants or other species could potentially act as additional reservoirs, although their epidemiological contribution is still limited (Hidayat *et al.*, 2021; Nugroho *et al.*, 2022). Environmental factors, such as humidity, temperature, and population density, also influence the stability of the virus in the environment and its transmission efficiency (Khodakaram-Tafti and Farjanikish, 2017).

Risk factors

The presence and spread of BVDV is influenced by several risk factors, including virus characteristics, animal immune status, farm management, and biosecurity practices (Bulcha *et al.*, 2025). One key factor is the presence of PI animals in the population (Stephenson *et al.*, 2017). PI animals continuously shed the virus through saliva, urine, genital secretions, and feces, increasing the risk of horizontal transmission and maintaining the cycle of viral endemicity in the herd (Chamorro *et al.*, 2011).

Dense farm management or intensive production systems increase the frequency of contact between animals, accelerating the spread of the virus (Yarnall *et al.*, 2025). Reproductive practices, such as artificial insemination with untreated semen or mating with infected animals, are also important risk factors (Demil *et al.*, 2021). Furthermore, the use of unsterilized equipment and facilities and the movement of livestock between farms without BVDV screening increase the likelihood of iatrogenic infection and cross-herd transmission (Evans and Reichel, 2021).

The immune status of each animal influences its susceptibility to infection (Nonnecke *et al.*, 2014). Calves or young cows that have not been previously exposed to the virus and have not been vaccinated are at higher risk of infection and can potentially become PI if exposure occurs early in pregnancy (Fulton, 2013). Conversely, herds with high vaccination coverage and passive immune protection from the mother can reduce the risk of clinical infection, although this does not necessarily prevent subclinical infection (Antos *et al.*, 2021).

Environmental factors also influence the spread of BVDV (van Roon *et al.*, 2020). High stocking densities, poor ventilation, high humidity, and inadequate sanitation can increase the persistence of the virus in the environment and facilitate transmission (Nelson *et al.*, 2016). In some cases, interactions with wild ruminants or other domestic species may act as additional sources of infection, although their contribution to the overall epidemiology is relatively small compared to PI animals (Rana *et al.*, 2025b).

Economic impact

BVDV has a significant economic impact on the cattle industry through both direct and indirect losses (Houe, 2003). Direct losses include decreased milk production, reduced growth of beef cattle, mortality, and the cost of treating sick animals due to acute infection or secondary complications (O'Donoghue *et al.*, 2025). The presence of PI animals exacerbates these impacts, as they continue to shed the virus, increasing the risk of infection throughout the herd (Graham *et al.*, 2016).

The impact of BVDV on reproduction also causes significant economic losses (Heuer *et al.*, 2008). Abortions, embryo resorption, the birth of fetuses with congenital abnormalities, and temporary or permanent infertility reduce herd reproductive efficiency, prolong calving intervals, and reduce the number of live calves (Grooms, 2004). This decrease in reproductive productivity directly impacts farmer income, particularly in dairy production systems that rely heavily on continuous calving and lactation (Arnaiz *et al.*, 2021).

Indirect losses include the costs of disease control, such as mass vaccination, identification and elimination of PI animals, and biosecurity and

livestock health monitoring (Gethmann *et al*., 2019). Reduced meat and milk quality due to subclinical infection, coupled with limited market access due to BVDV's endemic status, also increase the economic burden (Mwacalimba *et al*., 2025). In some countries, losses from BVDV can reach tens to hundreds of millions of US dollars annually, depending on prevalence, cattle population size, and the effectiveness of control programs (Zhang *et al*., 2022).

Vaccination

Vaccination is a key strategy in controlling BVDV and plays a crucial role in reducing infection prevalence, preventing the development of PI animals, and mitigating the economic impact of the disease (Antos *et al*., 2021). BVDV immunization programs are designed taking into account the virus biotype, herd immune status, and prevention objectives, both to protect individuals and to build herd immunity (Hu *et al*., 2026).

There are two types of BVDV vaccines commonly used: the modified-live vaccine (MLV) and the killed vaccine. The MLV vaccine can stimulate a strong humoral and cellular immune response and provide faster protection against acute infection (Perkins-Oines *et al*., 2023). However, its use in pregnant animals is limited due to the risk of abortion or the birth of a PI fetus if not administered correctly (Taberner *et al*., 2024). In contrast, the killed vaccine is safer for pregnant cows, although it usually requires a booster dose to achieve optimal protection and elicits a relatively weaker T cell response than the MLV (Stevens *et al*., 2009).

Vaccination success is influenced by the genetic diversity of BVDV, including the subgenotypes BVDV-1, BVDV-2, and HoBi-like pestivirus (Deng *et al*., 2020). These antigenic differences can impact vaccine effectiveness and increase the likelihood of breakthrough infections if circulating strains are not covered by the vaccine used (Yeşilbağ *et al*., 2017). Therefore, vaccine selection should consider the regional epidemiological profile and the dominant subgenotypes present in the herd (Rana *et al*., 2025b).

An effective vaccination strategy includes early immunization of calves before they are naturally exposed to the virus, administering booster doses, and implementing a coordinated herd vaccination program (Hu *et al*., 2026). Implementing vaccination, along with the identification and elimination of PI animals, enhanced biosecurity, and strict reproductive management, can significantly reduce virus circulation and reduce the risk of outbreaks (Moennig and Becher, 2018).

Treatment

To date, there is no effective specific antiviral therapy for BVDV. Clinical management is supportive, aimed at alleviating symptoms, preventing secondary complications, and maintaining the animal's physiological condition during infection (Robi *et al*., 2024). Supportive therapy includes oral or intravenous rehydration to address diarrhea-related dehydration, adequate nutrition, and monitoring electrolyte and acid-base balance (Van Metre *et al*., 2008).

BVDV infection often causes immunosuppression, making animals more susceptible to secondary infections by other bacteria or viruses (Hou *et al*., 2025). In this situation, antibiotics or antimicrobials are administered selectively to control opportunistic infections, while adhering to the principles of appropriate drug use to avoid triggering resistance (Dobos *et al*., 2024). The use of non-steroidal anti-inflammatory drugs (NSAIDs) may be considered to reduce fever and inflammation, but should be tailored to the animal's condition and potential side effects (Hägglund *et al*., 2024).

In PI animals, treatment is unable to clear the infection. PI animals continue to serve as reservoirs of BVDV and are a major source of virus spread (Hu *et al*., 2026). Therefore, a more effective control approach involves identifying and removing PI animals from the herd, along with vaccination, enhanced biosecurity, and sound reproductive management (Newcomer *et al*., 2015).

Control

Controlling BVDV requires an integrated approach that includes identifying PI animals, vaccination, implementing biosecurity measures, and maintaining good reproductive management to suppress virus circulation within the livestock population (Moennig and Becher, 2018). This strategy emphasizes preventing horizontal and vertical transmission and eliminating primary sources of infection to sustainably reduce disease prevalence (Isoda *et al*., 2025). Figure 3 illustrates an integrated control strategy based on the four pillars of BVDV: identification and elimination of PI animals, vaccination to increase herd immunity, implementing strict biosecurity measures, and effective reproductive management.

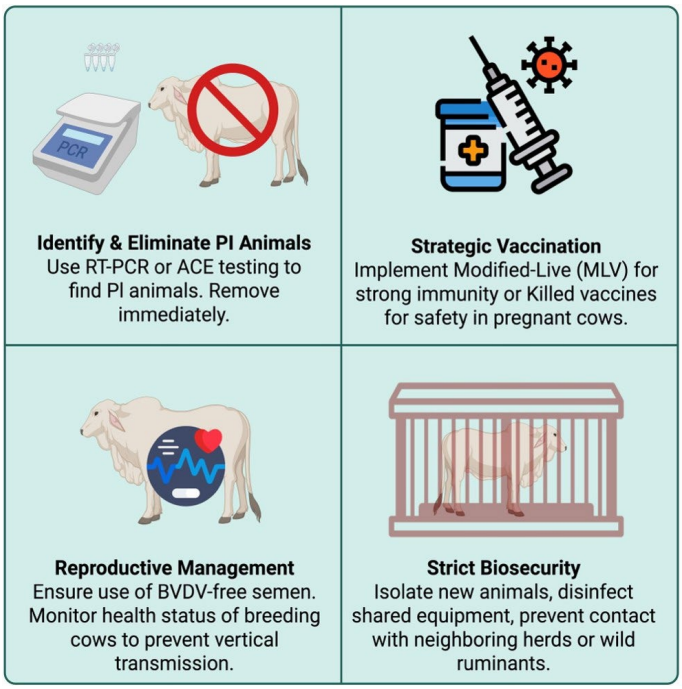

Figure 3. The 4-pillar control strategy.

Detecting PI animals through viral antigen identification or RT-PCR is the initial step in BVDV control (Strous *et al*., 2025). PI animals must be immediately isolated and removed from the herd because they act as the primary reservoir that maintains the virus in the population (Moennig and Yarnall, 2021). Routine herd screening and strict monitoring of new animals entering the farm are crucial to prevent the virus from entering (Khodakaram-Tafti and Farjanikish, 2017).

Vaccination is a key component of the BVDV control strategy, aiming to strengthen herd immunity, reduce clinical symptoms, and prevent the development of PI animals (Taberner *et al*., 2024). The choice of vaccine, whether modified-live or inactivated, must be tailored to the animal's immune status, age, and reproductive status (Newcomer *et al*., 2017). Implementing a planned immunization program, including boosters and vaccination of young animals before natural exposure to the virus, increases the effectiveness of long-term control (Antos *et al*., 2021).

Implementing biosecurity and reproductive management also plays a crucial role in reducing the risk of BVDV transmission (Sajeeb *et al*., 2025). Biosecurity measures include isolating new animals, disinfecting equipment, controlling livestock movements, and preventing contact with wild animals or other uncontrolled herds (Nugroho *et al*., 2022). Meanwhile, proper reproductive management, including monitoring the reproductive status of dams and using BVDV-free semen, helps prevent vertical infection and the birth of PI animals (Bisschop *et al*., 2025).

Conclusion

BVDV is a major pathogen in cattle that significantly impacts herd health, reproduction, and economics. The virus exhibits genetic and biotypic diversity that influences clinical symptoms, immune responses, and vaccination effectiveness. BVDV transmission occurs through both horizontal and vertical routes, with PI animals serving as the primary reservoir. Its distribution is global and influenced by livestock management practices, biosecurity, and control policies in each region. Effective control strategies include identification and removal of PI animals, planned vaccination, biosecurity implementation, and sound reproductive management. A thorough understanding of the pathogenesis, epidemiology, and risk factors of BVDV provides a crucial foundation for implementing effective herd management programs while mitigating the economic impact of this disease.

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Conflict of interest

The authors declare that there is no conflict of interest.

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