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Infectious Bursal Disease Virus a Comprehensive Review of Challenges and Advances in Poultry Health

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Abstract

Infectious Bursal Disease (IBD), caused by the Infectious Bursal Disease Virus (IBDV), is a highly contagious and economically significant disease affecting poultry worldwide. The disease is characterized by high morbidity rates, variable mortality, and severe impacts on flock productivity. The emergence of very virulent (vvIBDV) and novel variant strains has heightened the complexity of its epidemiology, challenging traditional control measures and vaccination strategies. Since its initial identification in Gumboro, Delaware, in 1962, IBDV has evolved, spreading across continents and generating diverse strains, including recombinant and reassortant forms. These evolutionary dynamics, coupled with the virus's ability to evade maternal and vaccine-induced immunity, underscore the pressing need for innovative approaches to disease management. This review provides a comprehensive overview of IBDV, focusing on its etiology, epidemiology, pathogenesis, and control strategies. Recent advancements in understanding the virus's evolutionary patterns and the development of novel vaccines are highlighted. Additionally, the review explores the challenges posed by hyper-virulent and variant strains, emphasizing the importance of integrating molecular and epidemiological data to inform effective interventions. By enhancing our knowledge of IBDV, this work aims to support the development of sustainable solutions for mitigating its impact on poultry health, ensuring the productivity and resilience of the global poultry industry.

Keywords: Infectious Bursal Disease (IBD); the Infectious Bursal Disease Virus (IBDV); sustainable solutions for mitigating; poultry health

1. Introduction

Infectious Bursal Disease (IBD), caused by IBDV, is a highly contagious viral infection that primarily affects young chickens. It poses a significant threat to the poultry industry worldwide, leading to substantial economic losses. It has a direct impact on mortality, from 5% to 30%, depending on the degree of protection of the birds and the form of the disease [1]. IBD is highly contagious, causing up to 100% morbidity in affected flocks. The hypervirulent strains of the virus can induce 100% mortality in specific pathogen-free (SPF) chickens, though overall mortality rates vary. [2]. The classical strains cause up to 20% mortality. Severe infection can cause mortality up to 25% in broilers and 60% in layers. In subclinical cases, the flock income will be reduced due to weight loss and increased FCR [3]. It became apparent that mild vaccine strains no longer provide adequate protection, as very virulent (vv)IBDV strains can overcome the immunity induced by highly attenuated vaccines [4].

The first case of IBDV was reported in Gumboro, Delaware in 1962 [5], subsequently spreading across the United States and Europe during the 1970s [6]. The virus's epidemiology became increasingly complex with the emergence of "variant" strains in the Delmarva region, capable of evading maternal immunity and potentially resulting from extensive vaccination practices [7]. By 1988, vvIBDV strains emerged, causing up to 90% mortality and rapidly spreading across Europe and globally [8], From 1985 to 1992, avirulent (avIBDV) took the United States as the spreading center and migrated to Canada, Mexico, South America, and central China, respectively. This is consistent with the first report and isolation of an avIBDV strain BX in China in the late 1990s [9]. Since 2009 or around, avIBDV has experienced about 10 years of a latent period since it was first introduced into

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China, and then the novel variants (nvIBDV) have emerged [10]. Subsequent research has extensively documented the virus's evolutionary dynamics, highlighting the emergence of variant, recombinant, and reassortant strains [10, 11]

In conclusion, IBDv is a highly contagious viral infection that poses significant challenges to the poultry industry. Understanding its etiology, epidemiology, pathogenesis, and control measures is crucial for effective management and prevention. This review aims to provide a comprehensive overview of IBDv, highlighting current knowledge, recent advancements, and potential future research and control strategies directions. By improving our understanding of IBDv, we can strive to mitigate its impact on poultry health and ensure the sustainability and productivity of the poultry industry.

2. Molecular Architecture and Protein Functions of Infectious Bursal Disease Virus

IBDV is a highly contagious virus that primarily infects young chickens, causing significant economic losses in the poultry industry. Classified under the family Birnaviridae and the genus Avibirnavirus, IBDV is a non-enveloped, double-stranded RNA virus with a bipartite genome comprising segments A and B [12]. Unlike other dsRNA viruses, birnaviruses lack an active inner core for transcription and instead organize their genome into ribonucleoprotein complexes (RNPs) formed by VP1-dsRNA, unbound VP1 (free VP1), and VP3 proteins. These RNP complexes are essential for initiating productive IBDV replication [13], resembling replication and transcription complexes in certain ssRNA viruses [14, 15]. VP3 protein, consisting of 258 amino acids (32 kDa), is multifunctional. It engages in homotypic interactions [16, 17] and interacts with both pVP2 [18, 19] and VP1 [17, 20, 21]. VP3 plays a dual role in virus replication and morphogenesis it functions as an RdRp transcriptional activator [20] and suppresses the host's RNA silencing mechanisms [22, 23]. During viral morphogenesis, VP3 acts as a scaffolding protein, assembling with pVP2 for capsid formation and recruiting VP1 and viral RNA for encapsulation [18]. VP4 is also encoded within this large ORF, and it is translated to the protease protein which is a non-structural protein involved in viral RNA replication [24]. VP2 and VP3 are the major structural proteins in IBDV, constituting 60% and 35% of the virion, respectively [25]. The smaller ORF of Segment A encodes VP5; a small non-structural protein that is implicated in viral pathogenicity as it accumulates at the plasma membrane inducing cell lysis [21]. Segment B, is the shorter segment with approximately 2.9 kilobases, and encodes a single protein known as VP1, which serves as the RNA-dependent RNA polymerase required for viral replication. The VP1 protein is crucial for the transcription and replication of the viral genome [4].

2.1. IBDV Classification from Traditional Serotypes to Modern Genomic and Antigenic Analysis

IBDV is classified into two primary serotypes, serotype 1 and serotype 2, based on the antigenic characteristics of the VP2 protein. Within each serotype, multiple genotypes have been identified, determined by the nucleotide sequences of the VP2 gene. The genetic diversity observed in IBDV is attributed to the virus's high mutation rate and the occurrence of recombination events among different strains. Structural proteins, notably VP2 and VP3, are critical for maintaining the stability of the viral particles [26].

While both serotypes exist, only serotype 1 has been shown to exhibit pathogenicity in chickens [27, 28]. Historically, IBDV strains have been categorized into four phenotypes based on their pathogenicity and antigenic properties classic [5], variant, very virulent [8], and attenuated. Due to the ongoing genetic evolution observed in the hypervariable region of the VP2 gene, seven major genogroups of IBDV have been proposed, which include classical, antigenic variant, very virulent IBDV (vvIBDV), distinct IBDV (dIBDV), variant/classical recombinant, as well as Italian (ITA) and Australian strains [29]. However, this classification has predominantly focused on the VP2 protein, even though VP1 also contributes to the pathotype and genetic evolution of IBDV. Recently, a new classification system has been introduced that considers both genomic segments of IBDV [11]. Segment A is divided into nine genogroups (A1 to A8 for serotype 1 and A0 for serotype 2), while segment B is classified into five genogroups (B1 to B5), irrespective of serotype. This results in a theoretical potential for 45 distinct reassortant forms of IBDV.

Genotypic classifications of IBDV do not fully capture the nuances of antigenic variation and cross-reactivity within the virus. Recent studies utilizing antigenic cartography have identified several antigenic clusters within serotype 1 of IBDV, demonstrating significant antigenic relatedness among some genetically distant viral strains [30]. These findings highlight the necessity of employing cross-virus neutralization assays, underscoring that reliance solely on genotypic classifications may be insufficient for understanding the virus's antigenic diversity.

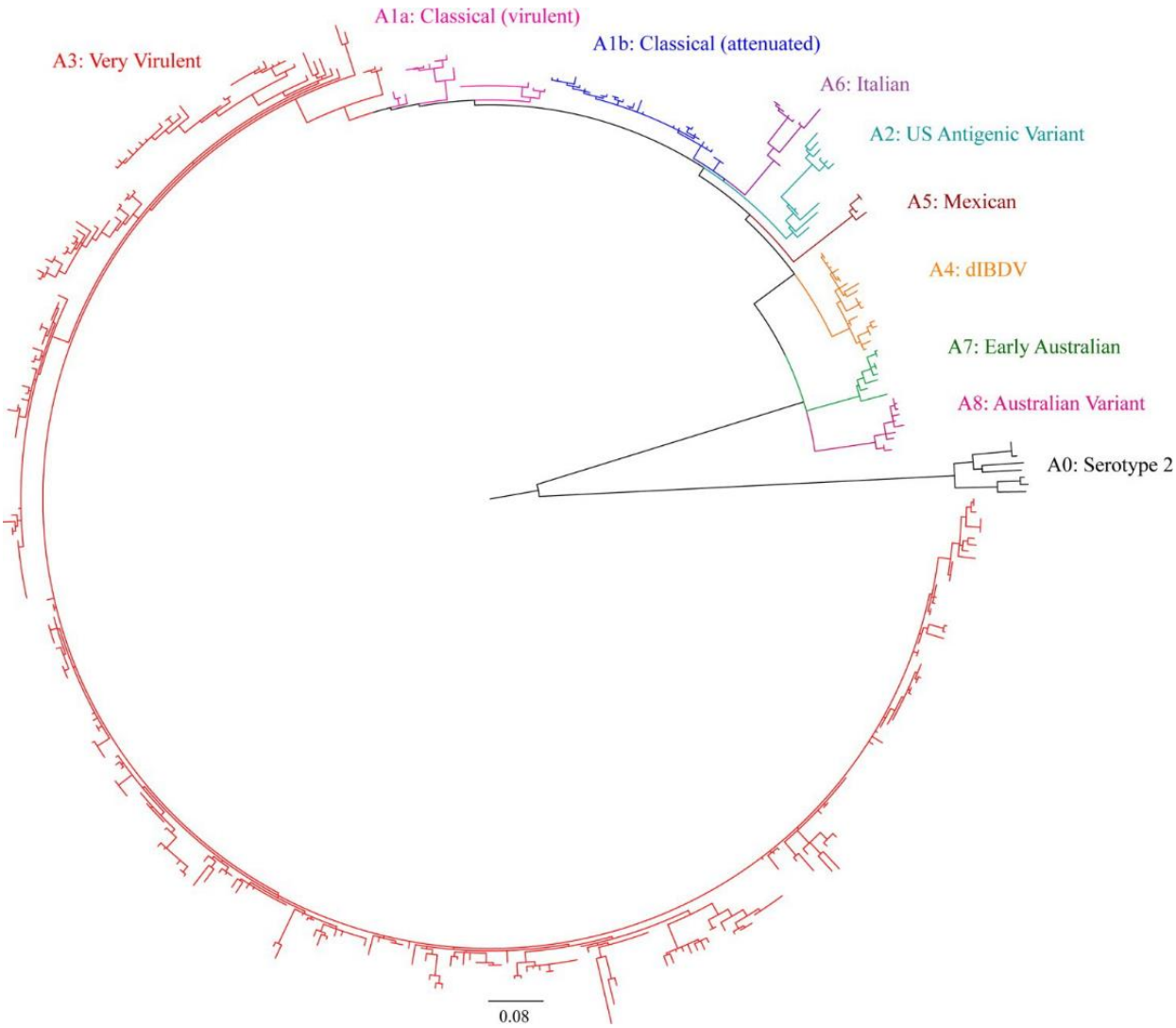

Figure (1) Circular phylogenetic tree of 463 IBDV strains based on the VP2 hypervariable region (nucleotides 785–1150) of segment A based on Islam [11].

3. IBDV Entry, Replication, and Egress

The viral entry mechanism of IBDV involves recognizing and attaching the viral capsid protein. Several proteins on the cell surface are involved in the entry of IBDV into the cell [31]. Recently, the chicken transmembrane protein cluster of differentiation 44 (chCD44) had been implicated to promote both the binding and entry ability of IBDV in B lymphocytes, acting as a cellular receptor for IBDV [32]. Cellular internalization of IBDV occurs by clathrin-independent endocytosis [33-35]. IBDV infection is dependent on entry in the early endosomal compartment and requires calcium loss and acidification for membrane penetration [35]. The low calcium concentrations in the acidified endosomal compartment trigger the release of small peptides (pep46 that remains associated with the virion after C-terminal processing of pVP2) from the virions that deform the membrane and lead to the formation of pores allowing ribonucleoprotein complex release into cytoplasm [36].

Unlike other dsRNA viruses, birnaviruses lack an active inner core for transcription and instead organize their genome into ribonucleoprotein complexes (RNPs) formed by VP1-dsRNA, unbound VP1 (free VP1), and VP3 proteins. These RNP complexes are essential for initiating productive IBDV replication [13], resembling replication and transcription complexes in certain ssRNA viruses [14, 37]. This structural organization implies that birnaviruses may represent an evolutionary link between single-stranded positive-sense RNA (+ssRNA) viruses and dsRNA viruses [38]. IBDV specifically utilizes the viral protein VP3, which binds to phospholipids on the cytosolic leaflet of endosomal membranes, facilitating replication within these compartments.

IBDV replicates in specialized cytoplasmic virus factories (VFs), where segmented dsRNA genomic material can undergo genetic reassortment, however the mechanism is still unclear [39]. The VFs are localized in the cytosolic side of endosomal compartments, containing VP1 (the viral polymerase), VP3, and the dsRNA

genome [40]. They are the sites of de novo viral RNA synthesis, and grow infection due to the accumulation of synthesized viral components [41]. Viral assembly occurs within single-membrane compartments closely associated with endoplasmic reticulum (ER) membranes [42]. At the early stage of infection, virus egress occurs through a non-lytic egress mechanism which increases the virus dissemination speed [43]. Later on, there is a drastic reduction of viral metabolism accompanied by remarkable increase in the virus-induced cytopathic effects (CPE) and increase of cell death [43].

4. IBDV Epidemiology Transmission Patterns, Environmental Stability, and Wildlife Vectors

The epidemiology of IBD revolves around the spread and persistence of IBDV in poultry populations. The virus has been reported in both developed and developing countries, with outbreaks occurring in commercial farms, backyard flocks, and wild bird populations [2]. The prevalence of IBDV varies across regions and can fluctuate over time. Outbreaks may be sporadic or occur in endemic or hyperendemic patterns. The presence of multiple antigenic variants and serotypes contributes to the persistence and reemergence of IBDV in different areas [44]. Understanding the factors' influencing transmission is crucial for implementing effective control measures and preventing outbreaks.

One of the key factors enhancing IBDV transmission is its strong environmental resilience. As a non-enveloped virus, IBDV can survive for extended periods outside a host, making elimination challenging. Studies indicate that IBDV remains infectious in poultry housing for up to 122 days and in feed and water sources for 52 days [45]. Therefore, routine sanitary measures must be rigorously followed to control IBDV. This point is crucial towards IBDV control and shall be discussed thoroughly in the control section of this review.

IBDV is primarily transmitted through direct and indirect contact. Direct transmission occurs when infected birds shed the virus through feces, saliva, or respiratory secretions, and healthy birds encounter the infectious material. Factors such as temperature, humidity, and organic material can influence the virus's survival outside the host. Even though birds primarily shed IBDV through their faeces, there is a risk of the virus being spread by air, especially at the ambient environment [46]. Vertical transmission from infected hens to their offspring is a significant mode of IBDV transmission. The virus can cross the eggshell during egg formation, infecting developing embryos. Infected chicks can hatch with the virus and serve as a source of infection for susceptible birds [47]. Indirect transmission can occur through contaminated fomites such as equipment, clothing, feed, and water sources. Contaminated premises and equipment can act as reservoirs, facilitating the transmission of IBDv to susceptible birds. Several risk factors contribute to the spread of IBDv. These include inadequate biosecurity measures, proximity to infected flocks, introduction of new birds or contaminated materials, and poor hygiene practices. High bird density and intensive production systems also increase the risk of transmission within poultry populations.

Wild birds, including migratory waterfowl, have been identified as potential carriers of IBDv [48]. They can introduce the virus to poultry flocks through direct contact or by contaminating the environment with their droppings. IBDV genome sequences have been detected in free-living pigeon and guinea fowl populations in Africa, suggesting that wild birds may play a role in IBDV ecology [49]. Virological studies show that IBDV has been identified in a range of bird orders, including Anseriformes, Columbiformes, Galliformes, Passeriformes, and Pelecaniformes, with isolates related to strains infecting poultry. Serological data indicate moderate exposure of wild birds to IBDV, highlighting their potential role as vectors. The detection of IBDV in healthy migratory birds suggests that these wild species could contribute to the virus's long-distance spread and genetic diversity. Although a definitive wild reservoir host remains unidentified, these findings underscore the need for continued surveillance of IBDV in wild bird populations to deepen our understanding of its epidemiology [48].

5. Genetic Diversity and Evolutionary Dynamics of IBDV Global Perspectives

Understanding the molecular epidemiology of IBDV is crucial for tracing the virus's evolution, assessing its genetic diversity, and identifying patterns of pathogenicity across regions. Studies conducted in various countries across multiple continents have shown that IBDV isolates often belong to different genetic lineages. Many of these strains include highly virulent forms and reassortant variants, illustrating the genetic complexity of IBDV and its adaptability to selective pressures such as vaccination [50-53]. The genomic elasticity for IBDV can be attributed to two major reasons the segmented nature which give rise to reassortant strains, and RNA nature which give rise to more frequent mutations along the genome.

The high variability in VP2 is partly due to intense vaccine-driven selection pressure on this major structural protein. Variability within the VP2 gene contributes significantly to the virus's genetic diversity and affects both immunogenicity and virulence. [28] found that IBDV strains from commercial poultry farms clustered into distinct molecular groups, emphasizing the extensive genetic heterogeneity of circulating IBDV strains in the field.

Genetic diversity studies of IBDV, particularly among very virulent strains, typically target the VP2 gene because of its role in both immune evasion and pathogenicity. However, there is growing recognition of the importance of other viral genes, especially those involved in replication and transcription, in contributing to IBDV virulence and transmissibility [54].

To investigate the dissemination and genetic evolution of IBDV, spatiotemporal phylogenetic analyses revealed that virulent strains were first identified in Iran in 1981, subsequently spreading to regions such as Western Europe, Africa, East Asia, the Caribbean, and South America [55]. These findings underscore the migratory dynamics of IBDV and highlight the significant influence of global poultry trade and farming practices on its transmission. Such reassortant strains arise from the genetic mixing of segments from different IBDV strains, leading to new viral genotypes with potentially altered virulence and immune escape characteristics [56]. Recent research has identified both very virulent (vvIBDV) and variant IBDV strains circulating in Egyptian poultry flocks. Study analyzed samples from 52 chicken flocks across various governorates, revealing that 38.4% tested positive for IBDV. Phylogenetic analysis of the VP2 gene's hypervariable region showed that five isolates clustered with vvIBDV strains, while one aligned with Chinese variant strains. These findings highlight the ongoing evolution and genetic diversity of IBDV [57].

6. Pathogenic Mechanisms of IBDV Bursal Targeting and Immune System Disruption

The pathogenesis of IBD is marked by a complex interaction between IBDV and the immune system of chickens, targeting specifically the bursa of Fabricius. This organ is critical for B cell development, making it a prime site for IBDV infection, which disrupts immune function and facilitates disease progression. Understanding these processes is vital for developing effective control measures [58].

IBDV typically enters through the respiratory or oral routes and subsequently infects the bursa of Fabricius. Here, it targets proliferating B lymphocytes, inducing apoptosis and ultimately leading to severe immunosuppression. IBDV's preference for B cells in the bursa leads to widespread lymphocyte destruction, with more virulent strains causing extensive bursal damage and heightened immunosuppression. Understanding IBDV's viral characteristics and mechanisms of infection is key for developing vaccines, diagnostic tools, and therapeutic interventions aimed at mitigating its impact on poultry health [59].

After entering the host, IBDV is carried by infected macrophages to the bursa, where it replicates within IgM+ B lymphocytes [60]. The infected bursa undergoes inflammation and releases cytokines such as IFN-γ, IL-6, and nitric oxide, further exacerbating bursal lesions [61, 62]. The virus also disseminates to other lymphoid tissues, including bone marrow, thymus, spleen, Peyer's patches, and caecal tonsils, which may sustain viral replication at later stages [63, 64].

At 48 hours post-infection, inflammation in the bursa becomes apparent, with cytolytic changes in infected IgM+ B cells by days 3-4. Between days 7-21, a marked reduction in IgM+ B-cell populations is observed, although IgA and IgG B cells are comparatively less affected [65]. While IBDV infection damages bursal follicular dendritic cells, reticular cells in the bursa and specific immune cells in the spleen show relative resistance, potentially preserving some immune functions [66, 67].

The virus's interaction with the host immune system further compromises defense mechanisms. Chickens, particularly those between 3-6 weeks old, experience severe immunosuppression after infection, making them vulnerable to secondary infections and reducing vaccine efficacy. Very virulent IBDV (vvIBDV) strains can result in up to 100% mortality in young chickens, with the damage to the bursa being largely irreversible [31].

A critical component in IBDV's pathogenesis is its attachment to the αvβ3 integrin receptor on B lymphocytes, which facilitates viral entry and replication. This process leads to extensive destruction of B lymphocytes and reduced antibody production, rendering birds more susceptible to other infections [68]. The immunosuppressive effects are both direct, through B lymphocyte depletion, and indirect, affecting cytokine production, lymphocyte trafficking, and cellular immune responses [69]. The age of the bird significantly influences the degree of immunosuppression, with younger birds experiencing more severe effects [70].

7. Clinical Manifestations, Pathology, and Diagnostic Techniques for Infectious Bursal Disease Virus (IBDV)

Clinical manifestations of IBD vary based on the age of the birds and the virulence of the IBDV strain involved. In young chicks, typically between 3 to 6 weeks of age, the acute form of IBD can be severe, with high mortality rates. Symptoms include depression, anorexia, watery diarrhea, ruffled feathers, hunched posture, reduced growth, and poor feed conversion. Birds also experience dehydration, weight loss, and lethargy, with mortality rates potentially reaching 100% in highly susceptible flocks. In older birds or under suboptimal vaccination conditions, the disease may present in a subacute or chronic form with less severe signs and lower mortality [71].

Acute outbreaks of IBDV often have a rapid onset with high morbidity and mortality that peaks quickly, followed by a recovery period of about five to seven days. Mortality rates vary significantly between strains, with some strains causing no mortality, while classical strains may reach up to 20%, and very virulent strains (vvIBDV) over 50%. The bursa of Fabricius (BF) is the primary site of pathological changes, displaying hemorrhages, swelling, and atrophy in affected birds [72].

On postmortem examination, the bursa of Fabricius often appears swollen, edematous, and discolored. Severe infections result in hemorrhagic and necrotic bursae, with significant reduction in size due to lymphoid follicle destruction [3]. Additional lesions may be observed in the spleen, thymus, and kidneys, and microscopic examination shows lymphocyte depletion and lymphoid follicle atrophy in the bursa of Fabricius (BF). A hallmark finding is the presence of intracytoplasmic inclusion bodies, termed Bursal Disease Virocytes (BDVs), within lymphocytes [73].

Lesion distribution and severity in IBD vary by strain and pathogenicity. Acute cases exhibit dehydration, hemorrhages in muscles, and visible lesions on the serosal and mucosal surfaces of the BF. Rapid bursal atrophy occurs within 7-8 days post-infection, often with or without inflammation depending on the strain. vvIBDV infections are marked by hemorrhagic inflammation, while variant strains generally lead to atrophy with minimal inflammation. Severe cases may display a yellowish hue on the BF serosa due to fluid accumulation from inflammation. Secondary renal involvement may result in distended kidneys, tubules, and ureters filled with urates, with inconsistently observed mucus in the intestine due to dehydration [74].

There are various laboratory methods used to detect IBDV, including virus isolation, antigen detection, and molecular techniques Virus isolation, although the most definitive diagnostic method, is not routinely performed due to the difficulty of adapting IBDV to cell cultures or embryonated eggs. It is important to note that not all strains follow the same growth characteristics. In general, IBDV strains can replicate in different systems from avian cell lines such as DF-1 [75] or mammalian cell lines such as Vero MC38 cells, and HD-11 [10, 76, 77]. Nevertheless, the majority of IBDV strains from clinical isolates do not replicate in those systems without adaptation [78, 79]. Primary cells also were explored for the propagation of IBDV including bursal cells [78] or CEF [80].

Antigen detection methods, such as agar gel immunodiffusion (AGID) and antigen-capture ELISA (AC-ELISA), can detect viral antigens in the bursa of Fabricius. These tests are particularly useful for early diagnosis, as they can detect IBDV antigens before the onset of antibody production [81]. Molecular techniques, such as reverse-transcription polymerase chain reaction (RT-PCR), provide a rapid and sensitive method for detecting viral RNA. RT-PCR can detect viruses that do not replicate in cell culture, as it does not require virus growth prior to amplification. For a comprehensive genetic characterization of IBDV strains, a combination of RT-PCR protocols targeting both segment A and segment B of the viral genome is recommended [82].

8. Differences between vvIBDV and nVarIBDV

Both very virulent infectious bursal disease virus (vvIBDV) and novel variant infectious bursal disease virus (nVarIBDV) significantly compromise the immune system of chickens, primarily through targeted damage to the bursa of Fabricius, a key organ for B lymphocyte development. Despite their shared focus on the bursa, vvIBDV and nVarIBDV differ markedly in the severity, timing, and mechanism of their immunosuppressive effects, as well as their capacity to evade immune responses [83].

vvIBDV induces rapid, intense bursal damage, with extensive lymphocyte depletion visible as early as 36 hours post-infection. This severe attack is accompanied by a heightened inflammatory response, characterized by elevated expression of inflammatory markers such as IL-6, IL-8, IL-18, NLRP3, and caspase-1 in infected B cells [84]. This inflammation, while part of the immune system's defense, exacerbates tissue damage, creating a hostile microenvironment that disrupts normal bursal function and amplifies immunosuppression. Consequently, vvIBDV's aggressive pathogenicity results in immediate and profound suppression of antibody-mediated immunity, leaving chickens acutely vulnerable to other infections [85].

In contrast, nVarIBDV produces a slower, less pronounced immunosuppressive effect, with visible bursal lesions and reductions in bursa-to-body weight ratios emerging around 48-60 hours post-infection. Although it still depletes B cells and induces inflammation, the impact is generally milder and more gradual than vvIBDV, suggesting a less aggressive pathogenic process [85]. However, nVarIBDV poses a unique challenge due to its ability to evade immunity established by vvIBDV vaccines. This immune evasion is likely linked to mutations in the HVR of the VP2 protein, a critical determinant of IBDV antigenicity. Alterations in this region may reduce the virus's recognition by antibodies produced in response to vvIBDV, leading to breakthrough infections in vaccinated flocks and complicating disease control strategies [75].

Both vvIBDV and nVarIBDV leave long-term immunological consequences beyond the acute phase. Persistent immunosuppression following infection compromises the immune system's response to secondary pathogens, increasing overall morbidity and mortality in infected flocks. Additionally, this immunosuppressive effect can diminish the efficacy of other vaccines administered to affected birds, posing a broader challenge to poultry health management [86, 87]. The comparative differences between vvIBDV rapid and intense immunosuppressive attack and nVarIBDV's gradual impact and immune evasion capacity highlight the need for further research into the molecular basis of these differences. Such insights will be essential for developing targeted interventions to counteract IBDV's evolving threat to poultry health.

The reassortant strains exhibited a lower mortality rate compared with the vvIBDV strains, which can facilitate their spreading. Despite lower mortality, the reassortant strains cause a similar degree of bursal atrophy and microscopic lesions as the very virulent strains. This indicates that they induce a comparable level of immunosuppression in infected chickens, making them susceptible to secondary infections and other health complications. The lower mortality rate of the reassortant strains might facilitate their spread within poultry flocks. With fewer birds succumbing to infection, the virus has more opportunities to transmit and persist, potentially leading to wider outbreaks. Furthermore, the unique genetic makeup of the reassortant strains, particularly the transIBDV-B segment, could pose challenges to existing vaccination strategies. Their higher genetic diversity might allow them to evade immune responses elicited by current vaccines, rendering them less effective [88].

9. Current status of IBDV evolutionary dynamics

9.1. VP2 sequence evolution analysis for IBDv

The VP2 protein of IBDV plays a critical role in viral infectivity, immune evasion, and antigenicity. Within the hypervariable region (HVR) of VP2, specific mutations and amino acid residues often serve as "genetic fingerprints" of very virulent IBDV (vvIBDV), distinguishing highly pathogenic strains [89]. The genetic evolution of VP2 is driven by point mutations, recombination events, and interactions with host proteins, enabling the virus to adapt to immune responses and environmental pressures. For instance, amino acid changes in the HVR can enhance viral fitness by modifying antigenic sites, allowing the virus to evade neutralizing antibodies in vaccinated or previously exposed poultry [90].

Four loop domains within the HVR—PBC (residues 219–224), PHI (315–324), PDE (250–254), and PFG (283–287) are pivotal in determining viral conformation and interactions with host immune systems. The PBC domain stabilizes epitope conformation, crucial for structural integrity and antigen presentation [91]. The PHI domain mediates immune recognition, with mutations allowing evasion of neutralizing antibodies despite immunization efforts [91, 92]. PDE and PFG are associated with host cell tropism and pathogenicity, with specific residues like 253 and 284 influencing viral infectivity and virulence [93].

Notably, the co-occurrence of residues 279D and 284A affects VP2 surface hydrophilicity, impacting viral stability, immune evasion, and infection efficiency in susceptible birds [94, 95]. Mutations in these regions also contribute to tissue culture adaptation and global dissemination. Strains harboring the 279D-284A combination have rapidly spread from West Africa, underscoring the evolutionary importance of these residues [55].

Although VP2 is central to IBDV pathogenicity, other viral proteins, including VP1, the polyprotein precursor (pVP2-VP4-VP3), and VP5, also influence virulence. These components interact with VP2 to regulate viral replication, structural stability, and immune evasion, offering a broader understanding of IBDV adaptation in diverse hosts [65].

9.2. Mutations at position 253 in hypervariable region associated with differential between IBDv strains

The cleavage of VP2, a critical capsid protein in IBDV containing key immunodominant epitopes, plays a pivotal role in viral replication, inducing neutralizing antibody production against the virus [26]. This region includes major hydrophilic peaks, A (212–224 aa) and B (312–324 aa), which are prone to mutations that affect virulence, adaptability in tissue culture, and the virus's antigenic profile. Such mutations can undermine the efficacy of several commercial IBD vaccines [96, 97].

Particularly, mutations at position 253 in the VP2 hypervariable region have been associated with variations in virulence and antigenicity among IBDV strains. Studies indicate that a single amino acid substitution at this position significantly elevates pathogenicity [98]. In addition, nonsynonymous mutations at amino acid 254 and certain synonymous mutations influenced the phylogenetic clustering of strains, especially within tropical regions [99]. Virulence declines when very virulent IBDV strains bearing mutations at 253 and 284 undergo serial passages in chicken embryo fibroblast cells, though pathogenicity is recoverable through reverse mutation [54].

The evolutionary significance of the VP2 hypervariable region has been emphasized, with key residues such as Gln at position 253, Asp279, and Ala284 being closely tied to virulence, cell tropism, and the pathogenic characteristics of virulent strains [100-102]. Additionally, mutations at 253, 279, 284, and 330 alter IBDV's antigenicity and virulence [41]. Specific amino acids at positions 253 and 284 are essential for cell culture adaptation histidine and threonine, while in vivo replication favors glutamine and alanine at these positions, highlighting a distinct selection mechanism during viral propagation [103].

9.3. Mutations associated with IBDv cell culture adaptation

Mutations play a pivotal role in enabling IBDV to adapt to cell culture conditions. Specific amino acid changes in the VP2 protein are critical for this adaptation. Histidine and threonine at positions 253 and 284 are essential for efficient replication in cell culture, whereas glutamine and alanine at these positions are favored during in vivo replication. This differential selection underscores the adaptability and flexibility of IBDV's VP2 protein under varying environmental pressures [103]. The extensive genetic diversity within VP2, driven by frequent mutations, reflects the virus's ability to respond dynamically to environmental challenges [54].

Adaptation to tissue culture is often facilitated through serial viral passage, a process that introduces specific mutations. Mutations within the hypervariable region (HVR) of VP2, located on the A-segment, are particularly associated with attenuated virulence and enhanced replication in cell culture [104, 105]. an Ala-to-Thr substitution at residue 284 enhances replication efficiency in cell culture. Similar substitutions at residues 279 and 284 have been linked to both adaptation and attenuation [106, 107].

Despite these findings, the mechanisms underlying IBDV's tropism for bursal B-lymphocytes and its adaptation to cell culture remain incompletely understood. One notable observation is that a point mutation in the α4β1 integrin ligand motif of VP2 can disrupt cell-binding activity in subviral particles (SVPs), thereby hampering viral recovery via reverse genetics without altering SVP structure [19, 104]. Furthermore, mutations in hydrophilic regions of VP2, specifically residues 212–223 and 314–324, drive antigenic variation, influencing both immunogenicity and virulence [41, 108].

In a highly virulent, cell-adapted IBDV strain, specific sequence alterations in the genomic segment encoding the precursor polyprotein have been identified as contributors to viral attenuation [94]. These findings collectively highlight the intricate interplay of genetic factors that enable IBDV to adapt to diverse environments and host systems.

9.4. Evolution dynamics of reassortment IBDv

Genetic reassortment is pivotal in the evolution of IBDV, with studies suggesting that reassortment is more significant than genetic recombination in the emergence of highly virulent strains [92]. Phylogenetic analyses have revealed distinct evolutionary pathways for the virus's two genomic segments, indicating that reassortment events have been crucial in the development of vvIBDV. Various forms of reassortment have been documented, including intersegmental exchanges between different IBDV strains, interserotypic reassortment between serotypes 1 and 2, and combinations that result in strains with novel triplet amino acid motifs and altered pathogenicity and antigenicity profiles [109].

Natural reassortant have been identified in both vvIBDV and other serotype 1 strains, as well as between serotype 1 and 2 strains, with a particularly high prevalence in southern China, where at least six distinct reassortant types have been characterized. Similar reassortment events have also been observed in field isolates from Nigeria, Europe, and other regions [79]. Phenotypic analysis of these reassortant strains shows that most exhibit intermediate virulence between very virulent and classical pathotype strains, offering valuable insights into the role of specific genomic segments in determining viral pathogenicity.

Point mutations during reassortment events can significantly influence IBDV pathogenicity and cell-binding capabilities. [104] Delgui demonstrated that a single point mutation in a triplet amino acid motif could abolish the cell-binding activity of IBDV-derived subviral particles, preventing the recovery of infectious IBDV via reverse genetics. Further studies have shown that viral pathogenicity can be affected by mutations in both genomic segments or through reassortment between segments [110, 111]. Noteworthy findings include the identification of reassortant strains with novel triplet amino acid motifs at positions 145-147 in Nigerian IBDV isolates [112]. These natural reassortment events between different IBDV strains have led to diverse genomic configurations, resulting in significant alterations in pathogenicity [113, 114].

10. Immunogenicity, immune evasion, and cross-protection

10.1. IBDv vaccinal and wild strain the immune response

Vaccination remains the primary defense against IBDV, but discrepancies between immune responses elicited by vaccine strains and those triggered by wild-type strains pose significant challenges. Research has explored various immune evasion mechanisms, revealing variability in immune responses and the effectiveness of different vaccine types. Infections with vaccine strains have been shown to induce distinct immunoreactivity and morphological changes in bursal follicles compared to wild-type strains [115]. Emerging IBDV strains may evade immunity conferred by traditional vaccines, resulting in variable mortality rates (5-40%) in affected flocks [116]. Different vaccine strains have also demonstrated varying immunopathogenic effects, with IBDV-B2 causing considerable immunosuppression and severe lesions in the bursa of Fabricius [117].The immune response to IBDV vaccination can also vary depending on the type of vaccine used. Vaccination with IBDV can induce either Th1 or Th2 polarization, reflecting a balance between cell-mediated and humoral immunity [118]. This polarization offers valuable insights into the adaptive immune response triggered by IBDV vaccines. Studies using ELISA techniques [119] have assessed immunoreactivity in vaccinated birds, comparing antibody levels and antigen reactivity in response to both vaccine and wild-type IBDV strains.

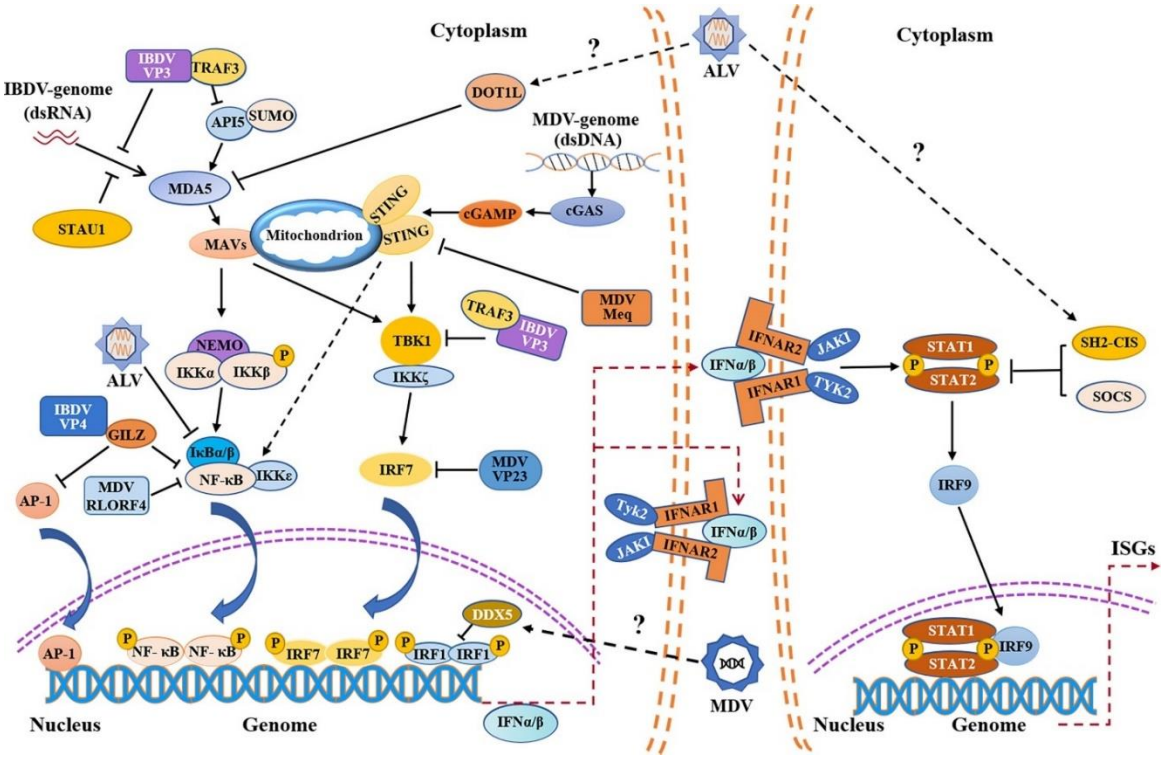

Figure (2) diagram of avian immunosuppressive viruses evading innate immune response in chicken [83].

Live IBDV vaccines are classified based on their breakthrough titers and virulence. Mild vaccines are characterized by low invasiveness but limited potential to generate a strong immune response. Intermediate and intermediate-plus vaccines, which are more virulent and have higher breakthrough titers, are more effective in overcoming maternally derived antibodies (MDA), but they carry an increased risk of immunosuppression [120]. Several studies have employed ELISA techniques to evaluate antigenicity and antibody responses to IBDV. Validated ELISAs for detecting antibodies against IBDV serotype 1 have been developed [121], and monoclonal antibody-based ELISAs have been used to assess IBDV antigenicity in different U.S. poultry flocks [7]. Recent advancements, such as the development of anti-VP3 antibody detection using plant-engineered VP3 protein [122], have enabled more precise detection of vaccine-induced immune responses.

However, some vaccine strains may fail to fully protect against IBDV infection, especially when virulent field strains with novel genetic profiles emerge. In field conditions, certain IBDV strains have caused only mild to moderate lesions while maintaining antigenic profiles similar to those of classical IBDV strains, suggesting partial immune evasion [123]. These findings underscore the need for continuous monitoring of both wild-type and vaccine strains for changes in antigenicity and pathogenicity, which will facilitate the development of better-targeted vaccines and more effective disease control strategies.

10.2. IBDV Post vaccinal reaction

Post-vaccinal reactions are a critical concern in using live attenuated IBDV vaccines, as they can lead to adverse effects and affect overall vaccine efficacy. Studies have shown that factors such as the virulence of the vaccine strain, the presence of MDA and timing of vaccination play significant roles in the severity and occurrence of these reactions [1].

The virulence level of live vaccine strains directly impacts post-vaccinal reactions. more virulent vaccine strains tend to cause more severe lesions in the bursa of Fabricius and lead to immunosuppressive effects, such as suppression of the mitogenic response [121, 124] Chickens vaccinated with a live IBDV strain showed gross and histological bursal lesions, including hemorrhage, cyst formation, and lymphocytic depletion, suggesting that higher virulence levels in vaccines can sometimes result in notable adverse reactions and even vaccination failures [125].

Despite the broad implementation of live IBDV vaccination in commercial broiler production, achieving consistent control over the virus remains challenging. Effectiveness of live IBDV vaccines and highlighted ongoing issues with vaccine-induced immunity, indicating that even with stringent vaccination strategies, IBDV control can be difficult in field conditions. This difficulty underscores the need for tailored vaccination schedules that consider strain virulence, timing relative to MDA, and possible local strain variations [126].

vaccination with IBDV can induce a Th1-Th2 immune response polarization, which provides insight into cell-mediated immune responses and can help in understanding the adaptive response in vaccinated birds. This immune polarization may affect susceptibility to other pathogens or influence the broader immune landscape of the bird post-vaccination [118].

10.3. Immune Evasion Mechanisms by Infectious Bursal Disease Virus

In chickens, where RIG-I is naturally absent, the detection of viral double-stranded RNA (dsRNA) primarily relies on chicken MDA5 (chMDA5). Upon IBDV infection, chMDA5 recognizes viral dsRNA, activating a signal transduction cascade that induces type I interferon (IFN-I) production, a crucial component of the innate immune response [127, 128]. However, IBDV has evolved mechanisms to evade this recognition. The viral protein VP3 can competitively bind to chMDA5 with viral dsRNA, inhibiting IFN-β expression and attenuating chMDA5-mediated interferon signaling, facilitating immune evasion [129]. Additionally, VP3 influences host protein modifications to suppress type I interferon signaling, further evading immune detection. Similarly, VP4 is implicated in bypassing innate immune responses [130-133].

IBDV also targets host proteins involved in pattern recognition receptor (PRR) signaling to avoid immune detection. Staufen1, a dsRNA-binding host protein, has been found to competitively bind to viral dsRNA with chMDA5, reducing IFN-β production and thus supporting IBDV replication [134].

Although there are no reports indicating that VP1, VP2, or VP5 directly regulate type I interferon pathways, VP2 and VP5 play crucial roles in viral release through apoptosis. IBDV, a non-enveloped virus, promotes its release by inducing apoptosis or autophagy in host cells. VP2 interacts with heat shock protein 90 (HSP90AA1) to trigger autophagy at an early infection stage, facilitating replication before autophagic responses are inhibited [135]. VP5, with dual roles in apoptosis, initially inhibits apoptosis by interacting with PI3K P85α to promote replication. Later, it induces apoptosis through interactions with VDAC2 and RACK1, leading to cytochrome C release and viral egress [54].

Moreover, IBDV may regulate host innate immune responses at the RNA level. Chicken p53 (chp53), a tumor suppressor and innate immunity regulator, is significantly upregulated during IBDV infection, enhancing antiviral gene expression and inhibiting viral replication [136]. IBDV manipulates this response via gga-miR-2127, which targets chp53's 3'UTR, down-regulating its translation and weakening the immune response. Additionally, gga-miR-142-5p targets chMDA5's 3'UTR, attenuating IRF7-mediated signaling and favoring IBDV replication [137]. Thus, IBDV evades host immunity by targeting both protein and RNA levels, enabling its persistence and proliferation in host cells.

10.4. Cross protection between IBDv strains

The issue of cross-protection between classical and variant IBDVstrains has long been a focus in IBDV research. Early studies found that standard strain vaccinations could offer full protection against variant strains when low challenge doses were used. However, the level of protection decreased with higher challenge doses. [27] observed that while classical and variant strains share protective antigens, cross-protection efficacy depends on the specific strains and the dose of both the vaccine and challenge virus. Supporting this, [7] developed monoclonal antibodies (mAbs) that can differentiate IBDV strains and identified that classical and variant strains share recognition sites for mAbs like R63, enabling some level of cross-protection [96].

Vaccination strategies have since evolved to enhance protection across diverse IBDV strains. Inactivated vaccines were shown to stimulate IBDV-specific T-cell and inflammatory responses in chickens [138], while post-hatch DNA priming followed by a killed vaccine boost provided protection against both homologous and heterologous strains [139]. Conversely, the rHVT-IBD vaccine, Vaxxitek, demonstrated only partial protection in specific-pathogen-free chickens, potentially due to insufficient IBDV antibody induction [125].

Given the presence of multiple co-circulating IBDV genotypes worldwide, developing vaccines with robust cross-protection is essential. [140] emphasized the importance of cross-protection in vaccine development, as new and variant genotypes emerge. A recent study demonstrated that recombinant VP2 protein (466 aa) expressed in E. coli provided complete protection against both nvIBDV and vvIBDV genotypes [141]. This recombinant vaccine's universal neutralizing epitopes might explain its broad protective capacity. However, the cross-neutralizing activity against vvIBDV genotypes remains limited, indicating that cellular immunity could play a significant role in enhancing cross-protection efficacy [142]. Further research is needed to assess whether nvIBDV vaccines can provide effective cross-protection across diverse genotypes.

11. Control section

11.1. Biosafety & Biosecurity

IBDV is known for its high contagion and resilience, which allows it to persist in poultry environments. Effective control of IBDV thus requires robust biosecurity and immunization strategies to reduce infection risk and manage outbreaks. Due to IBDV's resilience to inactivation, poultry farms implement stringent biosecurity programs. These measures include All-in/All-out production Introducing and removing all birds in a production cycle at once minimizes cross-contamination. Downtime between broods allowing a period between flocks reduces residual virus exposure. Comprehensive cleaning and disinfection Thorough decontamination of premises and equipment is critical, as routine disinfectants often prove ineffective against IBDV [143].

IBDV demonstrates remarkable pH stability, remaining viable between pH 2-12 and most stable at pH 3-9 [144], which necessitates comprehensive disinfection protocols for infected animal houses. Effective control requires a multi-step approach firstly, thorough physical cleaning to remove all organic matter, followed by application of chemical disinfectants such as quaternary ammonium compounds, 2% glutaraldehyde, 2-3% sodium hypochlorite, iodophors, or 1% formalin [145]. These should be applied using pressure sprayers with a minimum 10–20-minute wet contact time. The protocol should include high-pressure hot water washing, complete drying between steps, and particular attention to feeders, drinkers, ventilation systems, and all surfaces [146]. Post-disinfection measures include thorough rinsing if required, environmental sampling to verify effectiveness, and implementing a 2–3-week downtime period before restocking, along with strict biosecurity measures including controlled movement and footbaths. The virus has a global distribution, affecting poultry in diverse settings, including commercial farms, backyard flocks, and wild bird populations across both developed and developing countries [2].

Vaccination remains a cornerstone for controlling IBDV, given its ability to withstand common disinfectants. A well-structured vaccination program can prevent disease spread, though strict adherence to vaccination schedules is necessary for optimal protection [147]. [148] highlight that rational vaccination schedules, combined with biosecurity, are essential in IBDV control. The virus demonstrates exceptional stability, even under challenging conditions.

Studies on thermal inactivation indicate heat treatment at 56°C, IBDV remains viable for up to 120 minutes, though prolonged exposure of 300 minutes at this temperature can inactivate it [45]. Comparatively, other avian viruses like Avian Influenza, Infectious Bronchitis, and Newcastle Disease inactivate more rapidly, with shorter times required for complete neutralization [149].

Chemical Disinfectants sodium hypochlorite (0.5%) requires at least 60 minutes for effective inactivation of IBDV. While commonly used, adequate contact time is critical. Virkon-S concentrations of 1:200 and 1:400 effectively inactivated the virus within 30 minutes. Its efficacy supports its use as a potent disinfectant for IBDV control in farm settings. Comprehensive IBDV management combines preventive measures, monitoring, and research. Surveillance is essential for the early detection and containment of outbreaks. Additionally, research into viral persistence, genetic variability, and host interactions will inform future control strategies, potentially enabling development of targeted therapies and optimized vaccine formulations [149].

11.2. Vaccination Strategies

Vaccination programs are crucial for establishing protective immunity in poultry prior to exposure to IBDV, aiming to prevent or minimize infection severity and reduce subsequent immunosuppression. Enhancing

biosecurity, minimizing environmental stressors, and optimizing management practices are also essential for preventing and controlling IBD outbreaks. Investigations into the viral mechanisms of immune evasion, host susceptibility factors, and the interactions between innate and adaptive immunity are integral to developing more effective vaccines and control strategies [150].

12. Live Attenuated Vaccines

Live attenuated vaccines (LAVs) for IBDV are derived from classical virulent strains that have been weakened through serial passage in tissue culture or eggs, making them less pathogenic but still capable of inducing an immune response [151]. Based on their attenuation level, LAVs are categorized as mild, intermediate, or intermediate-plus ("hot" vaccines) [152-154]. LAVs stimulate both humoral and cellular immunity, mimicking natural infection and promoting protective antibodies and memory T cells. They can be administered via mass vaccination methods, such as drinking water, reducing labor (Mazariegos et al., 1990). Intermediate and intermediate-plus vaccines provide immunity even in the presence of MDA, which is crucial in young chicks. Although effective, intermediate-plus vaccines can cause immunosuppressive side effects, such as bursal atrophy, due to their pathogenic potential [155]. Environmental and immunological variability between farms can also affect their effectiveness. Additionally, MDA can neutralize the vaccine virus, diminishing its efficacy. Intermediate-plus vaccines are designed to overcome moderate levels of MDA, but optimizing vaccination timing based on MDA decay patterns remains critical [156]. Recent studies in India [157] suggest that certain vaccine strains, like the MB1 derivative, cause fewer bursal lesions and offer better health outcomes than conventional IBD vaccines.

The use of modified live vaccines (MLVs) remains vital for IBD control, with classifications based on virus attenuation levels—mild, intermediate, and intermediate-plus. The effectiveness of MLVs depends significantly on their ability to overcome MDAs, which offer early life protection but may interfere with early vaccination. MDAs exhibit a half-life of approximately 6.7 days in slower-growing meat chicks and around 3 days in broilers, with considerable variation depending on hatch and management conditions [158, 159].

12.1. Inactivated vaccines

Inactivated vaccines which use killed virus particles in conjunction with adjuvants, primarily elicit a humoral immune response by inducing antibody production against IBDV, without the risk of vaccine-derived pathogenicity [160]. These vaccines are safer, as they cannot replicate or revert to virulence, making them suitable for breeder birds. They boost antibody levels passed on to chicks, providing early immunity. However, inactivated vaccines require injection, making them labor-intensive and costly [45]. Typically administered in water-in-oil emulsions, inactivated vaccines are primarily used for breeders to generate high MDA levels in offspring, thus protecting them during their most vulnerable stages [161].

13. Genetically Engineered and Subunit Vaccines

Advances in molecular biology have enabled the development of genetically engineered vaccines, often targeting the VP2 protein of IBDV, known for carrying immunologically critical epitopes. These vaccines express key antigenic proteins, particularly VP2, either through genetic modification of attenuated IBDV strains or through recombinant DNA technologies [162]. The VP2 protein's structure allows for the induction of neutralizing antibodies. While genetically engineered vaccines hold promise, some still carry a risk of reversion to virulence, which is minimized through site-directed mutagenesis [163, 164]. Despite improvements, there is still a risk of reversion to virulence in some genetically engineered live IBDV vaccines, necessitating multiple mutations for safer, stable attenuated strains. Subunit vaccines expressing VP2 alone also require parenteral administration and may need booster doses, limiting their use in high-volume poultry settings. Although still in experimental or limited commercial use, subunit vaccines offer the potential for differentiation between infected and vaccinated animals (DIVA) strategy by enabling the detection of infection-specific [122].

14. Live Viral Vector Vaccines

These vaccines utilize vectors like the herpesvirus of turkey (HVT) or fowlpox virus to carry IBDV antigens, particularly VP2, to stimulate immune responses without the virus itself replicating [165]. The vector virus replicates within the host, expressing IBDV VP2 and inducing an immune response against both the vector and IBDV. HVT-based vector vaccines are less susceptible to MDA interference, making them ideal for early life vaccination [166]. Viral vector vaccines can be administered in-ovo or to day-old chicks, offering broad protection against classical and variant IBDV strains. They also avoid the risks of bursal damage or reversion associated with live vaccines [167]. Despite their benefits, vector vaccines are complex and require careful genetic engineering to maintain stability and efficacy. Additionally, viral vectors like HVT are known to face competition

from environmental pathogens in field settings, which can influence the vaccine's performance [168]. Vector vaccines provide high levels of protection against vvIBDV and certain antigenic variants even in the presence of high MDAs, making them increasingly popular in regions with diverse IBDV strains [169].

14.1. Immune Complex (Icx) Vaccines

Immune-complex vaccines, which combine an intermediate IBDV vaccine and antibodies, offer a unique intelligent vaccination approach through in-ovo administration, promoting a sustained immune response that bridges the gap as MDAs wane [170]. The viral-antibody complexes protect the live vaccine virus from immediate immune neutralization, allowing it to persist long enough to activate the immune system in young birds with high MDA levels [66]. This delay facilitates controlled release and immune response without triggering bursal lesions [171]. ICX vaccines can be administered in-ovo (into the egg before hatching) or subcutaneously at the hatchery, making them highly efficient for large-scale vaccination. They are particularly valuable for broilers with high MDAs that might otherwise neutralize standard live vaccines [172]. The production of ICX is complex, and their efficacy can vary depending on the antibody titers used. There are also logistical challenges in ensuring uniform application across flocks.

14.2. Subunit and DNA Vaccines

Subunit vaccines encoding the VP2 protein, have shown promise in various expression systems (Baculovirus, yeast, E. coli) [173, 174], with recombinant VP2-based vaccines now commercially available in some regions [175]. DNA vaccines, though still experimental, aim to provide both humoral and cell-mediated immunity but often require improvements for consistent efficacy [176].

Continued IBDV evolution, especially with vvIBDV strains, necessitates constant innovation in vaccine design. Strategies like the DIVA compatible vaccines could enable better disease tracking and management. Additionally, in-ovo vaccination methods are likely to see more adoption due to automation benefits, particularly for broilers. Genetic advancements may also support the development of multivalent vaccines that protect against multiple avian pathogens, streamlining poultry immunization programs and enhancing productivity. New advancements in biotechnology have introduced promising vaccines that mitigate previous limitations in IBD control strategies. Additionally, immunomodulatory agents are being explored to enhance immune responses and reduce IBDV's impact, improving flock resistance to infections [170].

14.3. Importance of vaccination timing in presence of maternally-derived antibodies

The timing and effectiveness of vaccination depend on MDA levels in chicks, which can interfere with the vaccine response. High MDA levels initially prevented effective vaccine-induced immunity in chicks, suggesting that the vaccination time should be at day 21, when MDA levels fall. Boosting at day 28, which enhances flock immunity, emphasizing the need for vaccination schedules that consider the decline of MDA [120]. MDA can interfere with vaccine efficacy and lead to variations in immune response. MDA levels could impact immune responses by blocking vaccine virus replication, particularly in young chicks, resulting in weaker immunity. This phenomenon was evident in chicks vaccinated in-ovo or post-hatch, where the presence of MDA delayed immune response development, potentially leading to an increased susceptibility to infection until antibodies waned to more optimal levels for vaccination [138]. The challenge with MDA was further observed in studies where IBDV vaccination occurred in 18-day incubation embryos. In these cases, passive antibodies were still retained in the yolk rather than circulating in the embryo, possibly increasing susceptibility to vaccinal infection, indicate that careful timing and consideration of MDA levels are essential for achieving optimal vaccine performance [138, 139].

15. Conclusion

In conclusion, IBDV continues to present significant challenges to global poultry production due to its highly contagious nature, the emergence of vvIBDV and novel variant strains, and its ability to evade both maternal and vaccine-induced immunity. The molecular epidemiology and genetic diversity of IBDV highlight its evolutionary dynamics, including mutations and the development of recombinant strains, which complicate efforts to control the disease. Understanding the differences between vvIBDV and novel variant strains, along with their immunogenicity and immune evasion mechanisms, is crucial for developing effective vaccines. The control of IBDV in poultry requires a multifaceted and integrated approach, combining effective vaccination, biosecurity, and management practices. Vaccination strategies, including live attenuated, inactivated, and genetically engineered vaccines, are central to controlling IBDV, each with its strengths and limitations. The timing of vaccination, particularly MDA, is critical for optimizing immune responses and ensuring long-term protection. As MDA

levels decline, proper scheduling and booster doses are necessary to enhance vaccine efficacy. Additionally, the virus's ability to evade immune detection through mechanisms such as inhibition of interferon signaling and manipulation of host protein responses underscores the need for continuous research into viral lifecycle and immune interactions. New vaccine technologies, such as viral vector vaccines and immune-complex vaccines, alongside advancements in biotechnology, offer promising solutions to overcome current challenges. The review emphasizes the importance of integrating molecular and epidemiological data to inform vaccination strategies, biosafety, and biosecurity practices. As the evolution of IBDV strains continues to pose threats, ongoing innovation and adaptation of vaccination protocols are essential to maintaining robust immunity in poultry and minimizing the impact of IBD outbreaks. By bridging the gap between research and control, we can work toward more effective vaccines and control strategies, ensuring better health and productivity in the global poultry industry and contributing to a more sustainable and resilient future for poultry production worldwide.

16. Ethics approval and consent to participate

Not applicable. This review article does not involve human participants, animal experiments, or any data collection requiring ethical approval.

17. Consent for publication

Not applicable. This manuscript does not contain any individual person's data in any form.

18. Availability of data and materials

All data and materials used in this review are publicly available and cited in the references section. No new datasets were generated or analyzed during the preparation of this manuscript.

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21. Authors' contributions

A.H.A.E. and **M.S.** conceptualized the review, designed the structure, and coordinated the writing process.
A.H.A.E., M.S., and **M.M.A.** conducted the literature review and drafted the initial manuscript, with a focus on the molecular architecture, epidemiology, and pathogenesis of IBDV.
A.A. and **M.A.** contributed to the sections on genetic diversity, evolutionary dynamics, and immune evasion mechanisms of IBDV.
M.M.A. and **A.A.** analyzed and synthesized data on vaccination strategies, biosecurity measures, and control practices.
M.A. provided critical revisions to the manuscript, ensuring scientific accuracy and coherence.
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