

MOLECULAR INSIGHTS INTO INFECTIOUS BRONCHITIS VIRUS PATHOGENESIS, HOST IMMUNE RESPONSE, AND IMPLICATIONS FOR VACCINE DEVELOPMENT

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ABSTRACT

Infectious bronchitis virus (IBV) is a highly contagious avian coronavirus that continues to pose significant economic and biosecurity challenges to the poultry industry worldwide. IBV causes multisystemic infections in poultry affecting the reproductive, respiratory, and renal systems, leading to significant economic losses. The virus demonstrates great genetic variety due to high-frequency mutations and recombination, giving rise to a multitude of variants that complicates disease control efforts. The pathophysiology and clinical relevance of IBV are rooted in its host-specificity, structural characteristics, and immune-evasion pathways. The avian immune system stimulates humoral and cell-mediated immunity in response to a subsequent antigen exposure. In addition to adaptive responses, IBV infection initiates innate immunological responses involving heterophils, macrophages, dendritic cells, cytokines, and complement proteins. Despite the use of live-attenuated and inactivated vaccines, IBV outbreaks continue to occur globally underscoring the shortcomings of current immunisation approaches. The evolution of IBV has presented obstacles for vaccine development, which have been addressed via DNA-based, recombinant, subunit, and reverse genetic vaccines. To reduce the burden of IBV, creative vaccination techniques must be designed with a thorough understanding of IBV-host interactions. This review highlights the significance of a thorough understanding of IBV-host interactions and the creation of innovative vaccination techniques to counteract this changing disease by combining the most recent findings.

Keywords: Infectious Bronchitis Virus, Pathogenesis, Host Immune Response, Respiratory disease, Vaccine

INTRODUCTION

Avian infectious bronchitis is a highly contagious disease of upper respiratory tract and poses a serious economic threat to the poultry industry. The disease is caused by the infectious bronchitis virus (IBV), a member of the genus *Gammacoronavirus*, family *Coronaviridae*, and order *Nidovirales* (Legnardi *et al.*, 2020). Clinical signs of the disease include mucus in the trachea and nares, sneezing, watery eyes, lethargy, tracheal rales, sneezing, and coughing. IBV causes a reduction in egg production and low quality egg production in layer (Cavanagh & Naqi, 2003). Infection with IBV produces tracheal ciliostasis and predisposes birds to secondary infections, further worsening the condition. Morbidity has always been 100 percent. However, mortality can range from 0% to 82 percent, depending on the age of the infected birds, immunological condition, virus strain, and secondary pathogen involvement (Ramakrishnan & Kappala, 2019a).

The viral genome is non-segmented and contains 10 open reading frames, with untranslated regions at the 5' and 3' ends. IBV is an enveloped virus with a lipid membrane surrounding the capsid and an overall diameter of 120nm. The virus produces 15 non-structural proteins (nsp2 – nsp16) and 4 structural proteins: membrane, envelope, spike, and nucleocapsid (Jackwood & de Wit, 2013). The most important protein is the club-shaped projection producing spike protein which gives virus its crown-like shape. Spike protein contains epitopes for neutralizing antibodies and plays an important role in viral attachment, plasma membrane fusion, and host specificity (Lai & Cavanagh, 1997).

Vaccination is widely used to enhance immune protection against IBV field strains. Both live attenuated and inactivated vaccines are commercially available. Due to the emergence of novel serotypes and widespread immunological failure, it is preferable to use local strains for vaccine development. The 4/91 and Massachusetts (Mass) are still commonly used in vaccine research around the world (Jordan, 2017). IBV can rapidly evolve due to genetic recombination and spontaneous mutations, as it is a positive sense single-stranded RNA coronavirus. Mutations in the spike gene lead to the formation of novel variants. Consequently, IBV is seen in a variety of antigenic variants and genotypic types (Bande *et al.*, 2015).

Description of the disease

Avian infectious bronchitis (IB) is primarily a respiratory infection. However, in field conditions, three major clinical outcomes are commonly observed: respiratory disease, reproductive disorders, and nephritis. Clinical manifestations vary depending on the age of the birds, the virulence of the viral strain, and the level of existing immunity.

Respiratory Disease

Difficulty in breathing, coughing, tracheal rales and sneezing with or without nasal discharge are the most common clinical signs found in broiler chicks aged two to six weeks. Affected birds often show generalized weakness, depression, reduced feed intake, and weight loss. Clinical signs in uncomplicated infections are usually mild and transient, lasting less than seven days in most cases (Wu *et al.*, 2024). The virus damages the mucosal lining of the respiratory tract, which predisposes birds to secondary bacterial infections. Common secondary pathogens include *Mycoplasma spp.* and *Escherichia coli*. Secondary *E. coli* infections are particularly common and exacerbate symptoms of upper respiratory tracts. The trachea is clogged with copious mucus on necropsy, pericarditis, airsacculitis and perihepatitis can also be seen in case of secondary *E. coli* infection (Chandravathi, 2021).

Reproductive Disease

Infection with the IBV, both at a young age and later in life, can cause reproductive issues in chickens. Clinical signs may not be evident in young hens but are more evident in adult chickens, or may appear as a minor respiratory sickness that goes unreported until the flock is thoroughly checked. Egg production usually begins to decline within seven to twelve days after infection. Typically, the decrease in egg production ranges from 3% to 10%, although reductions of up to 50% have been reported (Hassan *et al.*, 2023). As reproductive damage progresses, smaller eggs with poor shell quality and inferior internal egg quality are observed. Eggs may have pale shells, irregular shapes, or thin albumen (VALDEZ *et al.*, 2012). Flocks normally return to near-normal output within one week, although full recovery can take up to eight weeks. The oviduct may become shortened due to cystic oviduct formation, and ovarian regression may occur in some birds. If infection occurs in

chicks younger than 14 days of age, the oviduct may be permanently damaged, resulting in impaired laying capacity (Mueller, 2022).

Nephropathogenic Disease

In the nephropathogenic form of IB, mild respiratory signs are usually followed by systemic symptoms. These include depression, ruffled feathers, a slumped posture, reluctance to move, diarrhoea, increased water consumption, rapid weight loss, and wet litter (Calnek *et al.*, 1997). During necropsy, dark, dehydrated carcasses, enlarged kidneys and urate deposits in the urinary system may be observed (Mansur, 2018). These lesions are associated with the virus ability to infect and replicate in renal epithelial cells. Tubular damage reduces uric acid excretion and decreases the glomerular filtration rate, resulting in impaired kidney function. This results in hyperuricemia leading to precipitation of urate crystals on visceral

organs. Clinically, this condition manifests as visceral gout, a characteristic sign of nephropathogenic IBV infection (Liu *et al.*, 2015).

Gastro-intestinal Disease

Enteric IBV strains replicate and persist in the cecal tonsils and may also be isolated from duodenum and jejunum, causing intestinal lesions, particularly in the rectum. Although clinical sign caused by enteric IBV are usually mild or subclinical, some birds exhibit poor feeding, diarrhoea, wet litter, and stunted growth (Peek *et al.*, 2018). Replication of IBV in the intestinal tract facilitates horizontal transmission of the virus through fecal shedding. The gastrointestinal tract may also serve as a secondary site of viral persistence, allowing dissemination of the virus to other vital organs such as the kidneys and reproductive tract (Saif, 2007).

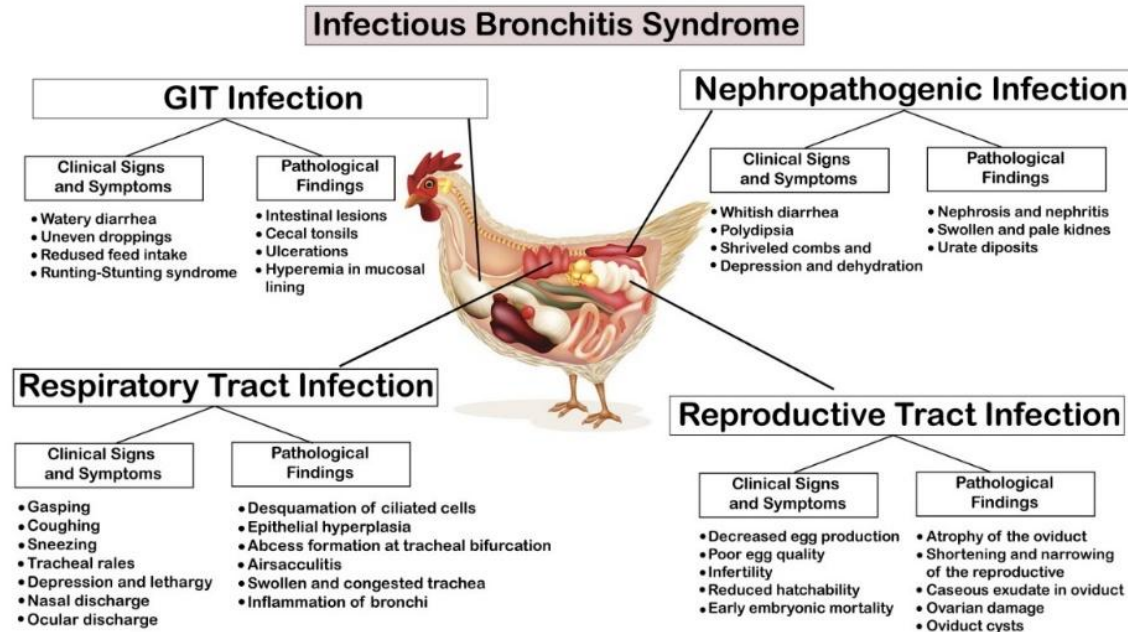


Figure 1 Clinical signs and symptoms and pathological findings linked with different pathological forms of IB disease

Physicochemical Characterization of IBV

Infectious bronchitis virus is a temperature sensitive virus. Exposure to 56 °C for 15 minutes or 45 °C for 90 minutes inactivates the majority of IBV strains. The virus is susceptible to common disinfectants as well as ether, chloroform, and other lipid solvents can also inactivate it. The virus's infectivity can be completely eliminated by treatment with a mixture of 50 percent chloroform (Saeed *et al.*, 2025). Infectivity can also be destroyed with 5% sodium hydroxide, 1:1000 mercuric chloride, 1:10,000 potassium permanganate, 0.1 percent formalin or 0.05 or 0.1 percent betapropiolactone (BPL) (Sylvester *et al.*, 2005). IBV is a UV-sensitive virus, and its infectivity can be destroyed by UV irradiation. Infectious bronchitis virus strains usually resist a wide pH range. They can survive at pH of 3 as well as pH 9 (Abdel-Moneim *et al.*, 2005).

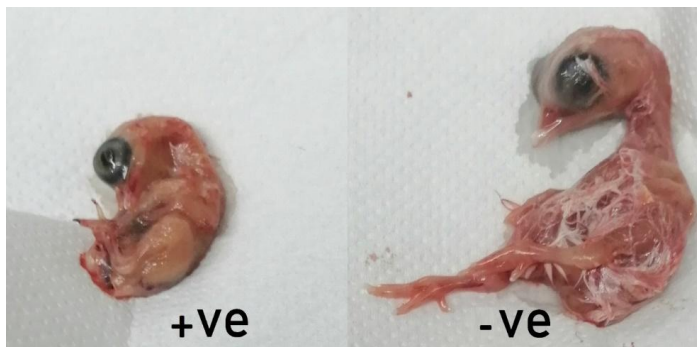


Figure 2 IBV positive chicken embryo showing gross changes typical to IBV infection, whereas, negative one showing normal growth of chicken embryo

Spike (S), membrane (M), small membrane (E), and nucleoprotein (N) are the four major structural proteins of virus. The spike protein is the most important structural

protein and is expressed as a densely glycosylated 1145-amino-acid protein that is cleaved into two subunits: the outer S1 (520 amino acids) and the membrane-bound S2 (625 amino acids) (Alvarado, 2004). The S protein controls cell and tissue tropism, facilitates viral entry, determines the viral host range, permits cross-species transmission, and enables the virus adapt to new hosts. The S protein consists of two subunits, S1 and S2. These subunits remain non-covalently bound in the virion, with S2 forming the base of the spike and S1 forming the crown of the spike. The S1 subunit is responsible for receptor binding, whereas the S2 subunit mediates the fusion of the viral envelope with the host cell membrane (Cai *et al.*, 2025). IBV entry is initiated when the S1 protein binds to the host surface glycans (alpha-2,3-linked sialic acids). After binding, furin-like or TMPRSS-type host proteases cleaves the S protein at the S1/S2 site, exposing the fusion peptide within S2. This cleavage enables insertion of the fusion peptide into the host membrane, followed by interaction of two heptad repeat regions (HR1 and HR2) and formation of six-helix bundles (Chan *et al.*, 2006). This six-helix bundle destabilizes the host lipid bilayer, resulting in formation of fusion pore through which viral genome is released in host cytoplasm (Bosch *et al.*, 2003). The M glycoprotein has a molecular weights ranging between 27 to 36 kDa, and is partially exposed on the viral surface, where it plays a role in viral assembly. The E protein is mainly localized in the Golgi apparatus of infected cells. This protein is involved in viral envelope formation, ion channel activity, viral assembly, budding, and apoptotic release of the virus from the host cell (Wilson *et al.*, 2006). The N protein is the most abundant viral protein and is responsible for binding the RNA genome to form a helical ribonucleoprotein (RNP) complex in mature virions (Nucleocapsid, 2013).

Non-structural Proteins of IBV

Non-structural proteins (nsp2–nsp16) of IBV are encoded by ORF1a and ORF1b and play important roles in viral replication, host modulation, and immune evasion mechanisms (Peng *et al.*, 2022). Due to the absence of natural nsp1, nsp2 is the first protein expressed in IBV. After viral infection, the eukaryotic initiation factor 2 (eIF-2α) kinase, also known as PKR, becomes active in response to viral dsRNA. Phosphorylation of PKR inhibits protein synthesis and drives the cell into an

antiviral defense state. Nsp2 has weak PKR-antagonistic activity, suggesting its involvement in viral replication and modulation of the host immune response (Gil & Esteban, 2000). The papain-like protease domain encoded in nsp3 cleave the polyprotein PP1a, releasing the mature viral non-structural proteins nsp2, nsp3, and nsp4. This protease also possesses deubiquitinating and deISGylating activities. By removing ubiquitin molecules, it delays the host innate immune response (Mielech *et al.*, 2014). Viral nsp4 induces membrane rearrangements that assist in the assembly of replication complexes and synthesis of viral RNA. These rearrangements also help protect viral RNA from host antiviral immune recognition (Doyle *et al.*, 2018). IBV nsp6 induces a restricted form of autophagy, which supports viral replicase assembly while preventing autophagy-mediated degradation of viral components (Maier *et al.*, 2013). The nsp7/nsp8 complex acts as a primase for nsp12 and plays an auxiliary role in viral RNA synthesis. In addition, nsp7 and nsp16 suppress dendritic cell maturation, cytokine secretion, and antigen presentation (Tan *et al.*, 2018). The nsp7/nsp8 complex acts as a primase for nsp12 and plays an auxiliary role in viral RNA synthesis. In addition, nsp7 and nsp16 suppress dendritic cell maturation, cytokine secretion, and antigen presentation (Gong, 2021). Notably, these non-structural proteins also contribute to the induction of host cell apoptosis during the later stages of IBV infection by modulating the intrinsic mitochondrial pathway. The expression of ORF1b alters the balance between pro-apoptotic and anti-apoptotic members of the Bcl-2 protein family. This process promotes activation of Bax and Bak while inhibiting anti-apoptotic proteins such as Mcl-1 and Bcl-XL. Consequently, caspase activation occurs, leading to controlled apoptotic cell death (Mandilara *et al.*, 2021).

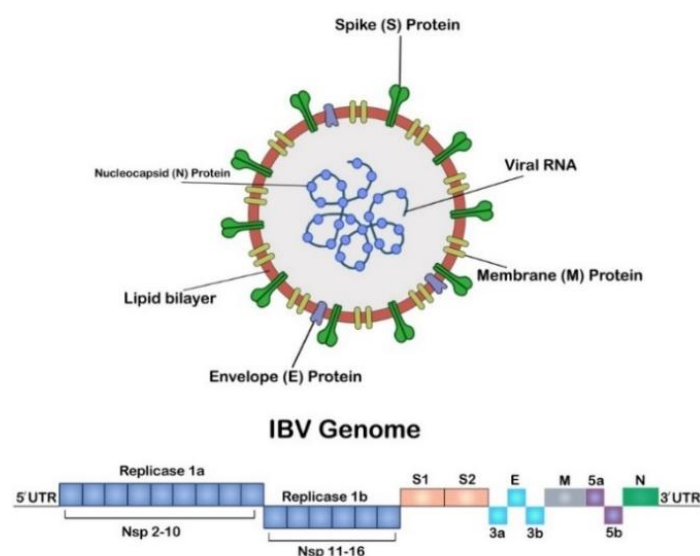


Figure 3 Morphology and genomic structure of IBV with viral genes for different structural and non-structural proteins

Host Immune Response to IBV Infection

The main focus of research on the immune response to infectious bronchitis virus (IBV) has been on the humoral immune response following IBV vaccination in chickens. In natural infections, a broader range of immune responses is observed, whereas vaccination generally induces a more standardized and uniform immune response. Local antibodies are believed to play a crucial role in protecting the epithelial lining of the respiratory tract from infection, even though serum antibody levels often do not closely correlate with protective immunity (Abozeid, 2023). Notably, chickens vaccinated against IBV and subsequently exposed to homologous IBV strains show increased expression of cytotoxic T lymphocyte (CTL)-related genes, including those encoding granzymes and perforin. This response has been strongly associated with improved protection of the tracheal epithelium. These findings highlight the important roles of both humoral and cellular immune responses in providing effective immunity against IBV in poultry. (Okino *et al.*, 2013).

Innate Immune Response

At the respiratory mucosa, IBV infection quickly sets off innate immune responses, such as the early recruitment of heterophils and macrophages and the generation of antiviral cytokines. IBV, on the other hand, actively opposes these reactions by interfering with antigen presentation and inhibiting type I interferon signaling, which promotes viral persistence.

Heterophils

In SPF hens, heterophil recruitment to IBV infection sites occurs quickly, peaking between 24 and 72 hpi. (Zhang *et al.*, 2021). They contribute to pathogen

containment during infection by releasing enzymes such cathepsin S and heterophil extracellular traps (HETs). More intense nasal exudation is correlated with lower heterophil counts, suggesting a protective effect in IBV infection (Kaore, 2018).

Macrophages

Studies conducted in vitro using the M41 strain reveal decreased macrophage function coupled with elevated IFN- α , IL-1 β , and IL-6 production, which eventually results in apoptosis and may help viral survival. (Kameka *et al.*, 2014). Although IBV infection reduces macrophage viability and phagocytic function, it causes significant macrophage infiltration in respiratory tissues (24–96 hpi). (Chhabra *et al.*, 2015). Studies conducted in vitro using the M41 strain reveal decreased macrophage function coupled with elevated IFN- α , IL-1 β , and IL-6 production, which eventually results in apoptosis and may help viral survival (Kameka *et al.*, 2014). (Sun *et al.*, 2021).

Dendritic cells (DCs)

Dendritic cell maturation and antigen presentation are inhibited by IBV (M41 strain), which may hinder T-cell priming and promote viral propagation. While antiviral cytokines are anticipated to be induced by PRR signaling, it is unclear how much IBV interferes with these pathways in avian DCs (Zuo *et al.*, 2021).

Natural Killer Cells

NK cell counts rise early after IBV infection, peaking in the blood and lungs at 1 and 4 dpi. Their exact role in viral clearance or illness regulation is yet unknown, despite this quick reaction (Vervelde *et al.*, 2013).

Complement system

IBV infection upregulates complement components (C1q, C1s, C3a receptor, and C4) while downregulating factor H in tracheal tissues, indicating activation of the classical pathway. The exact causes and functional effects of complement activation during IBV infection are yet unknown, though (Wurzner, 2003).

Acute Phase Proteins

Acute phase proteins are produced in the liver in response IBV infection and contribute to early immune modulation. Among these, mannose-binding lectin (MBL) has been strongly associated with disease outcome through activation of complement system. Reduced serum MBL levels correlate with increased viral replication, underscoring its protective role in IBV infection (Zhang *et al.*, 2017). In an *in vitro* study, MBL has shown the potential to bind to IBV and contribute to the immunological response following IBV vaccination. Two inbred chicken lines, L10H (high serum MBL) and L10L (low serum MBL concentration), were used. The addition of MBL ligands to the vaccine, particularly fructooligosaccharide, increased IBV-specific IgG production in high-MBL (L10H) chickens following a second vaccination, showing the contribution of MBL to improved immune responses (Kjærup *et al.*, 2014).

Cytokines

A strain-dependent cytokine response is triggered by IBV. Early in infection, proinflammatory cytokines like IL-1 β and IL-6 are persistently raised; higher levels of IL-6 are linked to nephropathogenic strains and the severity of the illness (Okino *et al.*, 2014). During infection with the Conn strain of IBV in laying hens, early downregulation of tracheal IFN- γ and IL-1 β mRNA was seen, followed by a marked increase in IL-1 β expression at later stages. This suggests a role of proinflammatory cytokines in altered eggshell component expression (Kameka *et al.*, 2014). On the other hand, some strains have shown early reduction of IFN- γ and IL-1 β , indicating IBV-induced immune regulation. Clinical symptoms can be postponed by exogenous IFN- α , demonstrating the significance of interferon responses in infection management (Pei *et al.*, 2001).

Apoptosis

IBV modulates apoptosis to optimize replication (Miller, 2005). The viral ORF1b region has been implicated in inducing apoptosis, while host regulators such as Mcl-1 and Bak influence the balance between cell survival and death (Li *et al.*, 2007). Disruption of this balance alters viral replication, indicating that apoptosis is a key interface in IBV–host interactions (Zhong *et al.*, 2012).

Adaptive Immunity

Adaptive immunity, also known as specific or acquired immunity, provides defense against IBV by activating B lymphocytes and T lymphocytes, and by producing memory cells, which play a significant antiviral role against IBV. It is classified into the humoral immune response and the cell-mediated immune response.

Humoral Immune Response

IgG (or IgY in chickens) is the primary circulating antibody, responds to IBV differently and more persistently than IgM. IgG can be detected in serum at 4 dpi, its level is highest at 21 dpi and can remain elevated for weeks. Following booster shots IgG levels rise dramatically as compare to primary response, but both responses follow the same pattern (Ramakrishnan & Kappala, 2019b). PBMCs and splenocytes after *in vitro* stimulation with IBV cause activation of memory B cells to produce antibodies at 21 dpi. IgG memory cells can be detected with ELISPOT as early as 3–7 days dpi in splenocytes and PBMCs infected with IBV Gray strain (Pei & Collisson, 2005).

In IBV infected chickens, IgA antibodies are present in the lamina propria and trachea, where they accumulated between the epithelial cells lining of trachea. IgA in these areas signifies a robust mucosal immune response against the virus at respiratory system infection (Maeda, 2022). Following vaccination of the live attenuated Ark DPI-type IBV vaccine, about ten days following vaccination IBV-specific IgA antibodies were found in lachrymal fluid. IgA levels were not considerably raised by subsequent challenges with the Ark-IBV isolate, suggesting IgA antibodies might help in neutralization of the virus during the challenge phase and lessen the severity of IBV infection (Joiner *et al.*, 2007). Live-attenuated H120 IBV vaccine after inoculation through ocular route triggered the presence of IgA-positive plasma cells in the Harderian gland (HG) by 14 days post-vaccination. Additionally, ocular vaccination of Ark-type IBV isolate, showed increase in IgA antibodies at 9 dpv in the HG (Gurjar, 2013). According to a study, large quantities of IgA are produced in plasma and lachrymal fluid after receiving the live attenuated Ark IBV vaccine by primary ocular vaccination. But as the exposure progresses, level of IgG start increasing and become dominant response thus lowering mucosal IgA level. This could make the Ark serotype more persistent and more vulnerable to IBV reinfection (Orr-Burks *et al.*, 2014). In chickens vaccinated with attenuated IBV-Mass, transcriptome analysis of tracheal samples revealed a significant rise in IgG at 5 and 8 dpi but a decrease in IgA expression at 8 and 12 dpi. Following secondary immunisation, this implies that IgG may be more protective in neutralising IBV in the upper respiratory tract, whilst IgA may be less important for preventing upper respiratory infections (Guo *et al.*, 2008). Numerous factors, such as the existence of several serotypes, the difference in virulence observed among strains, and the various symptoms of the IBV infection, make it difficult to study the mechanism and duration of the immune response to IBV.

Cell-mediated Immune response

Our understanding about the functionality of cell-mediated responses against IBV is lacking. Research on chicken CTL responses demonstrates that IBV infection lowers viral load and symptoms at an early stage, with CD8⁺CD4⁺ cells mediating lysis in a MHC dependent way (Schat & Skinner, 2022). IBV-specific CD8⁺ T cells were passively transferred to naive chicks to protect them from IBV (Hewawaduge *et al.*, 2024). Antigen-specific CTL activity began to appear at 3 dpi and peaked at 10 dpi in chickens infected with the nephropathogenic Grey strain of IBV. After 10 dpi, CTL activity decreased as IBV was controlled, and virus titer in the kidneys and lungs decreased (Seo *et al.*, 2000). With a considerable rise by 3–4 dpi, a peak at 5 dpi, and a return to baseline by 14 dpi, CTLs in the tracheal mucosa plays a significant role in early IBV clearance at this site (Okino *et al.*, 2013). Acute IBV infection can be reduced by effector CD8⁺ T cells, and chicks are significantly protected by transplanted primed $\alpha\beta$ T lymphocytes (Gurjar, 2013).

According to *in vitro* research, CTL activity causes IBV (Grey strain)-infected cells to lyse. CD8⁺ T lymphocytes are the main force behind this process, with CD4⁺ cells contributing just slightly, maybe as a result of different CD4⁺/CD8⁺ cell ratios (Collisson *et al.*, 2000). In one study, recipient chicks receiving donor CD8⁺ memory T cells were protected against acute IBV infection for the first four days after infection, and by day five, only minor clinical signs were seen (Chhabra, 2016). The modest protection provided by adoptive transfer of CD4⁺ T cells, on the other hand, was probably caused by the low levels of contamination by CD8⁺ T cells. This implies that CD8⁺ T cells play a more crucial role in the early stages of the immunological response to IBV (Seo *et al.*, 2000). The nucleoprotein of the IBV H52 strain included the first IBV-specific T cell epitope, IBV N71–78; only the S1 and N proteins elicited cytotoxic T cell responses. The CTL activity was restricted to the carboxy-terminal region of the N protein, and the M protein did not cause these kinds of reactions (Chhabra *et al.*, 2015). Increased numbers of CD4⁺ and CD8⁺ T cells were seen in PBMCs after vaccination with a DNA vaccine encoding the IBV N protein, suggesting a strong T cell response (Yan *et al.*, 2013). Cytotoxic cells like CTLs, CD8⁺ T cells, and NK cells generate cytotoxic enzymes like granzymes and perforin, which cause cell death of infected cells, helping the immune system fight against IBV (Vervelde *et al.*, 2013).

Passive Immunity

The idea of passive immunity to protect young chicks against IBV-induced oviduct abnormalities was first proposed as early as 1954. It was discovered that IgG antibodies, detected in both serum and respiratory mucus, provide protection to the

progeny when they are passed from vaccinated hens through the yolk (Kovacs-Nolan & Mine, 2012). Strong protection (>95%) against IBV was demonstrated in chicks with high levels of maternally derived antibodies at one day of age. However, this protection drastically decreased (>30%) after seven days. Rather than serum antibodies, local respiratory antibodies were associated more closely associated with protection. Live IBV-Mass vaccination at one day of age did not produce IBV-specific antibodies and caused a sharp drop in maternal antibodies, most likely as a result of neutralisation of the vaccine virus (Mondal & Naqi, 2001). Maternally derived neutralising antibodies provide substantial protection against viral multiplication in the kidneys and only limited protection against tracheal injury, according to recent investigations conducted on 6- or 10-day-old chicks challenged with IBV (D388 serotype, QX genotype). By combining heterologous live and inactivated IBV vaccinations, which increase the production of maternally derived antibodies, this protection was improved in SPF layer breeders (De Wit *et al.*, 2011). To protect hens during the laying season and ensure high antibody transmission to offspring, prime-boost immunisation regimens employ a live vaccine initially followed by an inactivated one (Chhabra *et al.*, 2015).

Vaccination

The major method of preventing infectious bronchitis virus (IBV) in chicken is still vaccination; however, the immunogenicity, range of protection, safety, and field usability of the various platforms vary significantly. Commercial usage is dominated by live-attenuated and inactivated vaccines because of their affordability and scalability, while recombinant technologies provide better specificity but have logistical and translational issues. Key trade-offs that affect vaccination selection in field settings are highlighted by a platform-by-platform comparison.

Live-attenuated vaccines

Infectious bronchitis in chickens can be prevented with first-generation vaccines called live-attenuated IBV vaccines. Normally, these vaccines are administered on the first day or during the first week of life via drinking water or spray. Due to their short-living immunity, a booster dose is needed two to three weeks after the first dose (Cavanagh, 2003). Maternal IgY antibodies, transferred from the breeder hen, circulate in serum and mucosal secretion of day-old chicks and may bind to and neutralize the live vaccine virus before they can replicate in respiratory epithelium. This reduces the antigen representation and limits the immune priming, necessitating booster vaccination (Ganapathy, 2021). Serial passage of IBV strains in embryonated chicken eggs (ECE) is used to attenuate the virus and reduce its virulence. Depending on the degree of attenuation, IBV vaccines can be either mild or virulent (Lin & Chen, 2017). Due to their low cost and ability to induce both local and systemic immune responses, live-attenuated vaccines are the most commonly used IBV vaccines. Respiratory and clinical symptoms may occur as post-vaccination reactions that last for a few days (Dhama *et al.*, 2014). Strain-specific Mass-strains like M41, Ma5, H52, and H120 are primarily covered by live vaccinations, along with additional monovalent vaccines like Conn 46, Ark 99, Florida, JMK, 4/72, and D247, respectively (Bhuiyan *et al.*, 2021). When IBV strains differ greatly in serotype or genetic lineage, live vaccines should not be used since this reduces vaccine effectiveness. Research indicates that the combination of H52 and H120 strains may provide prolonged cross-protection against a variety of IBV serotypes (Bijlenga *et al.*, 2004). To ensure broad protection against multiple IBV serotypes, day-old chicks (DOC) are commonly mass-vaccinated with one to three serotypes of live-attenuated IBV vaccines at hatcheries, followed by booster doses in longer-living broilers between days 14 and 18 to prolong immunity (Bhuiyan *et al.*, 2021). Certain live attenuated IBV vaccines may still retain residual virulence, which could cause tissue damage and raise the risk of airsacculitis, particularly under stress conditions. This tissue damage may progress to secondary bacterial infections or pathological abnormalities in day-old chicks (Gurjar *et al.*, 2013). Live-attenuated IBV vaccines effectively reduce virus shedding and generate both systemic and mucosal protection. They are ideal for large-scale chicken production because to their low cost and bulk administration by drinking water or spray. There is little cross-protection against heterologous IBV mutations, and protection is frequently strain-specific. Post-vaccination responses, tracheal injury, and an increased risk of subsequent infections can all be consequences of residual virulence. Additionally, maternal antibodies may hinder the reproduction of the vaccination virus, decreasing its effectiveness in the early stages of development. Their efficacy is heavily reliant on regional strain matching, necessitating ongoing monitoring. In endemic environments, there is still a danger of reversion to virulence and recombination with field strains.

Inactivated or Killed Vaccines

Inactivated vaccines are relatively safe, cost effective, and provide long lasting immunity without causing any post vaccination complications. These vaccines are either used alone or in combination with other IBV live attenuated vaccines. Inactivated IBV vaccines are made from IBV-infected allantoic fluid and are

formulated as oil-emulsion vaccines. These are usually given to broiler and layer breeders prior to the laying season (Go & Sansthan, 2014). Killed vaccines are typically administered intramuscularly or subcutaneously between 13 and 18 weeks of age. Inactivated vaccines are administered 4–6 weeks following the last dose of a live vaccine to achieve the best antibody titer (Ladman *et al.*, 2002). Because inactivated or killed vaccines don't replicate inside the host, they don't cause any pathological complications. However, these vaccines produce a short living humoral immune response and are unable to induce a strong cell-mediated immune response. Inactivated vaccines often need to be given as boosters following live attenuated vaccines. These require high doses of adjuvants, and may need multiple doses for effective immune response. Administering killed vaccines in large volumes can be challenging, as manual injection during vaccination can cause stress and may increase mortality, particularly in cases of accidental deep punctures in abdominal or thoracic regions. Their use in big commercial operations without preceding live immunization is limited by their dependency on each injection, which raises labor expenses, stress levels, and the possibility of administration mistakes.

Recombinant Vaccines

Viral-Vector based Vaccines

The ability of viral vectors to remain in cells without causing harms has led to study using viral vectors to deliver target genes. In order to provide prolonged antigen release, adenovirus vectors in particular have the ability to infect both dividing and non-dividing cells. They also enable the delivery of specific immunogenic protein components, which eliminates the need of developing vaccines using the full pathogenic organism (Tatsis & Ertl, 2004). Experimental designed recombinant vector vaccines against IBV have shown significant increase in the immune responses and protection against IB disease (Tan *et al.*, 2020). One study showed 90-100% protection against tracheal lesions after administration of a recombinant adenovirus vaccine containing IBV-S1-glycoprotein, followed by challenge with Vic S (serotype B) or N1/62- (serotype C-) IBV strains (Johnson *et al.*, 2003). In another study, the combination of chicken IL-18 with a recombinant fowlpox virus (rFPV) vector expressing the IBV-S1 gene increased antibody levels as well as CD4+ and CD8+ responses. Protection was 75% when the S1 gene alone was expressed in the vector. However, protection was 100% when IL-18 was added. This demonstrates that IL-18 may enhance immune responses when combined with viral vectors based vaccines (Chen *et al.*, 2010). Interference from maternally derived or pre-existing immunity, which can impair transgene expression, antigen uptake, and overall immune response efficacy, is a major challenge associated with viral vector vaccines (Faulkner *et al.*, 2013). Improper glycosylation, lack of proper protein folding, and inadequate post-translational modifications in host results in reduced immunogenicity due to alterations in antigen conformation and epitope arrangement. Targeted antigen delivery (such as S1 protein) is made possible by viral vector-based vaccinations, which can also elicit potent humoral and cellular immune responses. Additionally, they refrain from using live harmful viruses. The effectiveness of a vaccination can be greatly diminished by pre-existing or maternally acquired immunity to the vector. Widespread commercial use in poultry systems is also constrained by regulatory obstacles and manufacturing complexity.

Subunit and peptide-based vaccine

Subunit and peptide vaccines work by using specific protein segments or peptides derived from the pathogen to boost host immune response without exposing the host to the full pathogen. By cloning and expressing viral components in prokaryotic or eukaryotic expression systems, these vaccines offer protection with lower risk. Multi-epitope vaccines are also developed by focusing on immunogenic epitopes to elicit broader immune responses (Chen, 2010). The S1 and N-gene epitopes have been identified as targets for the production of CD8+ T-cell responses and neutralising antibodies. A recent study used several epitopes from the S1 and N protein genes to create an IBV vaccine. This peptide-based strategy achieved over 80% protection against viral challenge by eliciting strong humoral and cell-mediated immune responses (Yang *et al.*, 2009). Compared with birds vaccinated with only the S1 component, birds that received a double dose of the S1/S2 gene administered subcutaneously demonstrated superior protection against IBV (Eldemery *et al.*, 2017). In order to target IBV, a peptide vaccine strategy has been developed that combines polyclonal antibodies effective against multiple IBV strains with synthetic epitopes covering S20–S255 regions (Motamed, 2000). With the capacity to target conserved epitopes and facilitate logical vaccine design,

these vaccines provide excellent safety and antigen specificity. However, limitations with subunit and peptide-based vaccines include relatively low immunogenicity compared with live vaccines, the requirement for adjuvants or booster doses, and limited cross-protection. Additional challenges include technical complexity and higher cost associated with large-scale production and distribution for widespread use in poultry. Their poor cross-protection, high production costs, and technical complexity make them unfeasible for widespread poultry immunization programs.

Plasmids DNA Vaccines

A DNA plasmid containing genes encoding antigens that are subsequently produced in the host organism constitutes a plasmid DNA vaccine. These vaccines can be either monovalent, carrying a single antigen, or multivalent, carrying multiple antigens under a single promoter. Plasmid DNA vaccines can be used to provide targeted immune responses against several diseases or strains (Moreno & Timon, 2004). In contrast to the group that received only the multivalent plasmid vaccine, a study on DNA plasmids encoding IBV S1, N, or M proteins showed that recipients of multivalent plasmid vaccines followed by a single booster dose of a killed vaccine had significantly higher antibody levels and stronger immunity against IBV. Immune responses were improved by the prime-boost strategy, indicating increased effectiveness in preventing the infection (Yan *et al.*, 2013). Studies using monovalent and bivalent DNA vaccines encapsulated the S1 glycoprotein in chitosan-saponin nanoparticles enhanced immunogenicity and provided protection against homologous IBV strains (M41 or CR88). Furthermore, a study employing the pDKArkS1 plasmid vaccine, based on the S1 gene of the Arkansas strain, showed 100% protection when administered *in ovo* and followed by a live vaccine booster (Kapczynski *et al.*, 2003). S1-encoded DNA vaccines have been reported to induce strong immune responses, offering approximately 95% protection (Prompetchara *et al.*, 2021). DNA vaccines, especially in prime-boost techniques, can produce both humoral and cellular immunity and enable versatile antigen design. However, because plasmid DNA vaccines are typically administered intramuscularly, their large-scale application in commercial poultry production is limited. They are not suitable for mass immunization because they need intramuscular injection and delivery methods, which restricts scalability in commercial poultry.

Reverse Genetic Vaccines

Reverse genetics is a molecular genetics technique that examines how a gene functions by altering its nucleic acid sequences and analysing the resulting phenotypic consequences. Through the reconstruction of complete viral cDNA and the subsequent synthesis of infectious RNA to produce recombinant viruses, reverse genetics-vaccines enable precise modification of viral genomes (Lindenbach, 2022). The pathogenic S1 gene of the Beau-IBV strain was replaced with the S1 genes from the virulent M41 and European 4/91 IBV strains to create the Beau R-IBV vaccine. This alteration improves the safety and effectiveness of the vaccine by eliciting protective immune responses against IBV without generating a new pathogenic strain (Armesto *et al.*, 2011). After five passages in chicken embryos, the modified R-H120 IBV strain maintained high biological activity and generated high titers of haemagglutination inhibition (HI) antibodies when used as a vaccine. It demonstrated effective immunity without sacrificing safety, with a protection rate comparable to that of the conventional H120 vaccination (Zhou *et al.*, 2013). The production of safer, strain-specific vaccinations with better antigenic matching is made possible by the precise editing of IBV genomes made possible by reverse genetics. Despite certain difficulties, reverse genetics-based vaccines, which are resistant to neutralisation by pre-existing immunity, have the potential to greatly improve IBV immunisation strategies. However, further research is required to determine how these vaccines influence viral selection pressure and mutation rates. Their usage is currently confined to experimental or early-stage applications because of technical complexity, regulatory obstacles, and insufficient field validation. Despite issues with cross-protection and safety, live-attenuated and inactivated vaccines continue to be the mainstay of IBV management because of their scalability and affordability. Recombinant systems, on the other hand, provide better immunogenic targeting and accuracy but are restricted in their field application, cost, and delivery difficulties. A major obstacle in the development of next-generation IBV vaccines is still bridging the gap between experimental effectiveness and commercial viability.

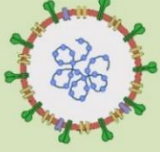
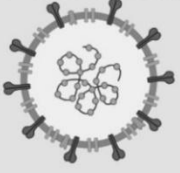
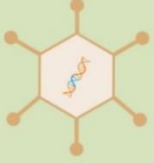
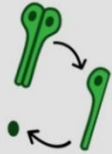
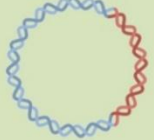
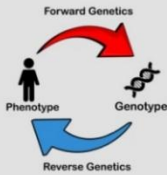
Type of Vaccine	Advantages	Disadvantages
Live-attenuated Vaccine 	Retains most of pathogen's immunogenicity, Strong and broad immune response, cross-protection, rapid immune response, ease of administration, cost effective and no adjuvant requirement	Potential reversion to virulence, limited strain coverage, maternal antibody interference, environmental stability, time consuming to manufacture, mutation and recombination effect
Killed Vaccine 	Heat stable, high safety, no viral shedding, broad implications, no virulence reversal, no interference from maternal antibodies, ease of quality control and reduced risk of adverse reactions	Poor immune response (just humoral), require multiple or booster doses, requirement of adjuvant, low mucosal immunity, reaction at injection site, cost complications and only strain-specific protection
Viral-Vector based Vaccines 	High safety and stability, rapid development, strong immune response, durable immunity, no additional adjuvant, lower cytotoxicity and ease of administration	Reduced immunity due to pre-existing immunity, Potential risk of infection, adverse reactions, chromosomal integration and oncogenesis, variable efficiency and cold chain storage requirement
Subunit and peptide-based vaccine 	High safety and stability, targeted (antigen specific) immune response, low risk of adverse side effects and ease of mass production	High requirement of antigen, complex preparation, no mucosal immunity, Multiple doses, limited to protein antigen, lower immunogenicity and requirement of adjuvant
Plasmids DNA Vaccines 	Cost effective, safe and long term stability, easy combination with adjuvants, possibility of oral formulation, multi-epitope potential, ease of manufacturing and robust immune response	Poor immune response, requirement of gene gun for administration, limited clinical validation, risk of genetic integration and immune tolerance in prolonged vaccination
Reverse Genetic Vaccines 	Precise genetic modification, rapid adaptation to emerging strains, full antigenic presentation, less side effects, reproducibility and stability	High cost, regulatory hurdles, high technical complexity, risk of genetic instability, limited cross protection, potential for recombination and requirement of multiple dosage

Figure 4 A summary of some important advantages and limitations linked with IB vaccine

Vaccine Development against IBV

Current IBV vaccination strategies rely primarily on live attenuated and inactivated vaccines to reduce clinical disease and viral shedding. These vaccines in conjunction with booster doses, are used to increase immunity and reduce respiratory epithelial reactions; however, their ability to stimulate robust and long-lasting mucosal immune responses in the respiratory tract remains limited (Hassan *et al.*, 2021). Heterologous live-attenuated vaccines, compared with homologous vaccines alone, provide a more rapid onset of immunity and broader cross-protection. However, live vaccines are associated with risks of reversion to virulence, recombination with field strains, and inconsistent protection against newly emerging genotypes. In contrast, inactivated vaccines are safer and more stable but require repeated booster doses and are poor inducers of mucosal and cell-mediated immunity (Lu *et al.*, 2025). A promising strategy for boosting mucosal immune responses is the combination of inactivated vaccinations with nanoparticles (Lopes *et al.*, 2018). Nanoparticles encapsulate viral antigens or inactivated vaccines and facilitates their delivery to mucosal-associated lymphoid tissues (MALT) in the respiratory tract. These particles enhance antigen uptake, promote sustained antigen release, and stimulate local immune responses, including secretory IgA production and T-cell activation (Jia *et al.*, 2015).

Different types of vaccines are used in different countries, each containing specific vaccine strain depending on the locally circulating isolates. The H strain of IBV was developed to provide wider cross-protection against different IBV serotypes by combining H52 and H120 strains (Bijlenga *et al.*, 2004). According to research, heterologous IBV vaccination strategies, particularly for the 793B variant, are effective against strains like Italy 02 and QX, and provide long-lasting immunity than live attenuated vaccines (Wit *et al.*, 2009). For serotypes such as Massachusetts, Connecticut, and Arkansas, as well as other strains of Georgia 98 and California, both modified live and inactivated IBV vaccines are available in North America (Umar *et al.*, 2016). Vaccines based on IB H120 and Holland variants (D274 and D1466) are commonly used in Europe. Immunity levels in the United States vary by geographic location and vaccine provider, with some cross-protection against strains such as Florida and JMK (Mondal, 2005). Furthermore, the combination of the IB Ma5 and IB 4/91 vaccines provides robust heterologous protection, whereas the high potency of the QX-type vaccines limits their use in Europe (Cook *et al.*, 2012). In Pakistan M41, D-274, D-1466, and 4-91 strains are the main target of vaccines due to their cross-protection potential (Rafique *et al.*, 2018). Regional vaccination programs are largely driven by locally circulating variants because of the extensive genetic diversity of IBV. While such approaches improve protection, they do not fully address the rapid evolution of IBV. This

highlights the need for platform-level improvements rather than continual strain replacement. New developments in vaccine technology, such as recombinant vector vaccines and nanoparticles delivery systems, have the potential to improve mucosal protection against IBV. Additionally, studies on novel mucosal adjuvants are being conducted to enhance the effectiveness and range of protection offered by existing vaccinations. Collectively, these advances represent a shift toward next-generation IBV vaccines designed to provide durable, cross-protective, and mucosal-targeted immunity.

CONCLUSION

Infectious Bronchitis Virus (IBV) continues to be a significant threat to the poultry industry since its first identification in 1931, causing widespread economic losses worldwide. Even with improvements in our knowledge of the virus' pathophysiology, host immune responses, and vaccine development, IBV remains challenging to manage. A significant obstacle to vaccine effectiveness is the virus's capacity for rapid mutation and the emergence of new genotypes, underscoring the necessity of ongoing surveillance and the development of modern immunisation strategies. Both humoral and cell-mediated responses are essential for infection prevention, and the immune response to IBV involves complex interactions between innate and adaptive immunity. Current vaccine strategies, including as DNA, recombinant, live-attenuated, and inactivated vaccines, exhibit promise but are constrained by concerns about cross-protection and the appearance of novel variants. More thorough defence against changing IBV strains might be provided use of reverse genetic technologies or target several viral antigens. Vaccination approaches that utilize reverse genetic technologies or target multiple viral antigens may provide broader defence against changing IBV strains. Identifying conserved viral antigens and immune correlates of protection should be the main goal of future studies aimed at better understanding the molecular interactions between IBV and the host immune system. The development of vaccines that offer broad-spectrum protection and can be adapted to accommodate the virus's rapid evolution is essential. Greater emphasis is needed on mucosal immunity, as effective induction of local respiratory and renal immune responses remains a critical gap in existing vaccination strategies. In parallel, sustained molecular surveillance is essential for rapid detection of emerging IBV genotypes and for guiding regional vaccine updates. A deeper mechanistic understanding of IBV–host immune interactions, particularly viral modulation of innate immune pathways, will be key to identifying novel therapeutic and prophylactic targets. Addressing these priorities through the integration of immunological, molecular, and epidemiological approaches will be key to the development of durable control strategies, reducing the economic burden of IBV and ensuring sustained poultry production.

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