IB and ND in Poultry

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Infectious bronchitis (IB) and Newcastle disease (ND) are among the most important viral diseases of poultry with substantial global economic impact . Infectious bronchitis is caused by the IB virus (IBV), a member of the Gammacoronavirus genus, family Coronaviridae, and subfamily Orthocoronavirinae. IBV is commonly referred to as avian coronavirus and it belongs in the same family and subfamily as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is currently ravaging the world, although the latter is in a different genus—Betacoronavirus. Newcastle disease (ND) is caused by ND virus (NDV), which belongs to the genus Avulavirus in the family Paramyxoviridae. Both viruses have genomes made up of single stranded RNA (ssRNA).

infectious bronchitis virus Newcastle disease virus Vaccine Immunity Poultry

1. Introduction

Infectious bronchitis (IB) and Newcastle disease (ND) affect poultry birds of all ages and breeds. The extent and severity of IB is pronounced in young chicks [1], when compared to older chicken, while ND though seen in chickens of all ages, has a more protracted course in older birds [2]. Crinion and Hofstad [3] reported that the severity of IB lesions is more pronounced in day-old chicks and decreased with increase in age of the chickens.

Humans are susceptible to Newcastle disease virus (NDV). This may cause mild conjunctivitis, reddening of the eye, excessive lachrymation, edema of the eyelids, sub-conjunctival hemorrhage, and laryngitis when exposed to large doses of the virus [4][5]. NDV-associated conjunctivitis usually resolves rapidly, but the virus could be shed in the ocular discharge for about a week. In some cases, mild, self-limiting flu-like disease could result. Other clinical symptoms such as chills, headaches, and fever, with or without conjunctivitis, may occur. Both the strains used in vaccines and virulent strains associated with poultry may infect and cause clinical signs in humans. Laboratory workers and vaccinators are mostly affected, but the use of personal protective equipment and bio safety cabinet has significantly minimized the exposure of laboratory workers. Infection is rarely seen in farm workers [6]. There is no evidence to support human-to-human transmission, but the potential for human to bird transmission exists [7]. Newcastle disease virus does not pose a risk to food safety.

Infectious bronchitis virus (IBV) poses no risk to human health as there is no evidence to suggest that humans act as reservoir for active replication of IBV. Also, there is no evidence of transmission from human to human, or human to animal. Though neutralizing antibodies have been documented in people working with commercial chicken flocks [18], the significance of the neutralizing antibodies remain unknown. Humans can only transmit IBV to poultry birds by mechanical means, by carrying virus on clothing from an infected bird or flock to uninfected

ones. A reported isolation of an avian IBV-like virus from humans was later shown to be a human Coronavirus isolate [8].

2. Immunity and Immune Response against IB and ND in Poultry

2.1. Vaccine-Mediated Immunity against IB and ND

2.1.1. Vaccine-Mediated Immunity against IBV

Live attenuated vaccines against IBV infection induce both humoral and cellular immunity in immunized hosts as demonstrated by several studies. Vaccination of chickens with live H120 alone or in combination with live CR88 induced high titers of IgY and IgA anti-IBV antibodies, CD4+ T cells, CD8+ T cells, and granzyme homolog A [9][10]. LDT3-A and 4/91 commercial live vaccines induced production of antibodies and CD4+ and CD8+ T cells in vaccinated birds [11]. Ocular vaccination with live attenuated IBV Ark-Delmarva industry vaccine induces IgA anti-IBV antibody as a primary response to infection while memory response to infection is dominated by IgY [12]. Vaccination of day-old broiler chicks with Massachusetts (Mass), 793B, D274, or Arkansas (Ark) induces significant high levels of CD4+, CD8+ and IgA bearing B cells in the trachea of birds [13]. Despite the capacity of live attenuated vaccines to induce both humoral and cellular immunity, they face the challenge of risk of spreading live vaccine virus. Therefore, other types of vaccines such as inactivated vaccines and/or DNA vaccines are considered as alternatives. Inactivated vaccine induces weak cellular immune response and requires priming with DNA vaccines. Priming with DNA vaccines encoding IBV structural genes and boosting with inactivated vaccines induce CD4+CD3+ and CD8+CD3+ T lymphocytes and memory B cells marked with high titers of IgY anti-IBV antibody [14]. More so, IBV-CS vaccine an inactivated IBV vaccine encapsulated in chitosan nanoparticles induced production of IFN-γ, IgA and IgY against IBV [15] and this is unlike the conventional inactivated vaccine, which only elicits limited mucosal immune responses. A combination of live attenuated vaccine and inactivated vaccine containing a BR-I IBV strain confer effective immune protection against infectious IBV strain through the induction of IgY anti-IBV antibodies and effector TCD8 cells and granzyme A [16]. It is believed that the induced anti-IBV IgY was as a result of the development of memory B lymphocytes after administration of live attenuated vaccine a day before re-vaccination with the oil adjuvanted inactivated vaccine, which upregulated IgY gene expression [17]. Full dose vaccination with H120 a live attenuated vaccine on a day-old chick showed full protection against IBV marked with high levels of IBV-specific IgY, IgA and cell-mediated immune genes including, IFN-γ, CD8+ T cells, and granzyme homolog A [18]. This suggests that for complete protection against IBV full dose vaccination is paramount. However, a study reported delayed production of IgA and IgY was observed in day-1 > day-7 > day-14-old chicks when vaccinated with live attenuated Arkansas Delmarva Poultry Industry-type (ArkDPI) IBV vaccine [17]. The authors, therefore, suggested vaccination to be carried out after day-7 post-hatch as the IgY antibodies from the day-1-old chicks had lower affinity and poor vaccine-mediated protection against IBV. More so, vaccination with an attenuated ArkDPI vaccine, elicited low systemic and mucosal antibody responses on day-1-old chicks compared to chickens vaccinated at a later stage in life. According to Saiada et al. [19], the populations of (CD)4+, CD8+, and CD4+/CD8+ T-cells increased with age and this pattern does not change with IBV vaccination.

Additionally, ArkDPI vaccines induced greater serum antibodies, B and T-helper cells (CD3+CD4+) and cytotoxic T cells (CD3+CD8+) on day-7 chicks compared with day-1-old chicks [20]. Another study showed that vaccinated chickens that presented high monocyte MHC II expression had the weakest vaccine-induced protection against IBV [21]. In the study, vaccine-induced MHC-II expression correlated with the viral load and response to IBV infection/vaccine varies among the MHC-B haplotypes, with some haplotypes being more resistant compared to the others [93]. Therefore, genetics could play a significant role in infection susceptibility/resistance and monocyte MHC II expression in vaccinated birds could serve as a marker to determine the protective effect of IBV vaccines. The use of DNA vaccines has been shown to induce both humoral and cell-mediated immune responses and could provide for complete protection against IBV infection. A chimeric multi-epitope DNA vaccine induced the production of antibodies, CD4+CD3+, and CD8+CD3+ T-lymphocytes in vaccinated birds [22]. A poly-epitope DNA vaccine consisting of B and T cell epitopes activated naïve B cells to produce neutralizing antibodies and elicited CD8+ T cells (CTL) response against IBV [23].

2.1.2. Vaccine-Mediated Immunity against NDV

NDV live attenuated vaccine (G7M) generated by reverse genetics induced high T-cell proliferation, IFN-γ, and antibodies [24]. VG/GA Newcastle live vaccine induced IgY and IgA anti-NDV antibody responses in vaccinated birds [25]. More so, VG/GA induced strong type I IFN (IFN-α and IFN-β) response in vaccinated chickens prior or post-NDV infection [26]. Inactivated NDV vaccine induced high levels of IL-6 and IFN-γ in vaccinated birds [27]. Vaccination with NDV attenuated vaccine (Nobilis ND LaSota; Cevac Vitapest L) and inactivated vaccine (Nobilis Newcavac) induced the production of anti-NDV IgY, IgM, and IgA in vaccinated birds [28]. NDV DNA vaccine encapsulated in N-2-hydroxypropyl trimethyl ammonium chloride chitosan (N-2-HACC) and N, O-carboxymethyl chitosan (CMC) nanoparticles induced IL-2, IL-4, IFN-γ, anti-NDV IgY and IgA antibodies in immunized birds [29]. NDV DNA vaccine encapsulated in Ag@SiO2 hollow nanoparticles (pFDNA-Ag@SiO2-NPs) induced IL-2 and IFN-γ in vaccinated birds [30]. More so, high titers of serum antibody were induced by NDV/LaSota-N-2-HFCC/CMC-NPs vaccine, and this vaccine significantly promoted the proliferation of lymphocyte and induced high levels of IL-4, IL-2, and IFN-γ in immunized birds [31]. The use of virus-like particle (VLPs) in vaccine production has proven useful as it could elicit both humoral and cell-mediated immune responses in immunized host. Moreover, VLPs mimics the structure of the wild-type virus and could be recognized by the host immune system. For instance, ND-VLPs stimulated the maturation of dendritic cells, upregulated the expression of MHCII, CD40, CD80, and CD86 and cytokine secretions including- TNF-α, IFN-γ, IL-6, IL-4 and IL12p70 in mice. The induction of IgY response and the presence of CD4+, CD8+ T cells indicate the efficiency of VLPs in inducing humoral and cellular immune response [32].

Considering NDV-IBV co-infection in birds, several studies considered developing NDV-IB chimeric vaccines and these vaccines have been demonstrated to be useful in combating mixed infections as shown by their ability to elicit both humoral and cellular immune responses in vaccinated birds. An N-2-HACC-CMC/NDV/IBV NPs and N-2-HACC-CMC/NDV-IBV NPs antigens (NDV and IBV) encapsulated with chitosan induced higher titers of IgY and IgA anti-IBV and anti-NDV antibodies in chickens, promoted significantly the proliferation of lymphocytes, induced high production of cytokines; interleukine-2 (IL-2), IL-4 and interferon-γ (IFN-γ) production in vaccinated chickens.

Increased levels of IFN-γ and IL-2 in the study was said to be as a result of higher induction of Th1 responses [33]. Chimeric infectious IB-ND-VLPs vaccine-induced anti-IBV and anti-NDV antibodies, T-cell cytokines, including- IL-4 and IFN-γ and this shows that chimeric IB-ND VLPs can evoke both Th1- and Th2-type cellular immune responses against IBV and NDV infections [34].

2.2. Immunopathology in the Hosts Resulting from IBV and NDV

2.2.1. Immunopathology in the Hosts from IBV

IBV causes severe lesions in the kidney [35], air sac [36] and trachea [37] in infected birds. Upon infection, IBV activates the Endoplasmic reticulum (ER) stress response and induces pro-inflammatory cytokines and apoptosis through its M protein. IBV M protein upon glycosylation enhances the activation of GRP78, an ER stress marker, which in turn activates PERK/IRE/CHOP/XBP1 for subsequent trigger of pro-inflammatory cytokines (IL-6 and IL-8) and apoptosis [38]. IBV distorts eggshell formation by reducing the expression of collagen type I gene in the thymus and CaBP-D28K in the uterus (genes related to eggshell formation in those regions, respectively) [39]. According to the authors, a marked infiltration of cytotoxic cells ((CD8+ and TCR-γδ+ T cells), cytotoxic substances (B-NK, perforin and granzyme) and pro-inflammatory cytokines was observed in the mucosa of the IBV-infected chickens [109]. Pro-inflammatory cytokines—IL-1β, IL-6 and IFN-γ—are said to play a major role in tracheal lesions in IBV-infected birds and the induction of CD8αα and Granzyme homolog A gene provides for protective immune response [40]. IBV-Beaudette induced apoptosis in chicken macrophage HD11 cells by activating caspase-8 and caspase-9 pathway through Fas/FasL and increased expression of Bax/reduced expression of Bcl-2, respectively [41]. More so, apoptosis is induced by IBV through the upregulation of pro-apoptotic growth arrest and DNA damage-inducible protein (GADD153) for its downstream function via the ER stress response pro-apoptotic pathways; protein kinase R-like ER kinase (PERK), eIF2α, activating transcriptional factor 4 (ATF4) pathway and protein kinase R (PKR) [42]. IBV infection also triggers the expression of p38 mitogen-activated protein kinase (MAPK) pathway, which also induces production of pro-inflammatory cytokines (IL-6 and IL-8) [43]. MAPK is also responsible for regulation of apoptosis in IBV and IBV infection induce phosphorylation of MAPK kinases 7 (MKK7) which induce the activation of JNK. Activated JNK promotes apoptosis in IBV-infected cells through modulation of Bcl2 family proteins or as a result of cell cycle arrest at the S and G2/M phases in IBV-infected cells [43][44]. It is important to note that although apoptosis is a non-specific defense mechanism that interfere with the replication of viruses in infected cells, it may cause tissue damage as a result of the premature destruction of the infected cells [41] and induce acute inflammatory responses and the inflammatory reactions may expose the host to bacterial infections [40]. The level of pro-inflammatory response depends on the IBV strain and the genetics of the infected host [45]. With the influx of pro-inflammatory proteins, the action of CD8+ T-cells and NOs produced by macrophages and/or dendritic cells in response to viral infections could induce severe lesions in infected hosts.

2.2.2. Immunopathology in the Hosts from NDV

Inflammatory responses induced by NDV in infected hosts usually leads to cellular apoptosis and tissue damage. NDV upon infection induce the secretion of high mobility group box 1 (HMGB1) that promotes the production of inflammatory cytokine storm. HMGB1 binds TLR2/4 and RAGE leading to downstream NF-κB activation and

cytokine production. More so, the HMGB1-RAGE interaction induced by NDV promotes the activation of ERK1/2 and JNK [46]. Oviductal dysfunction and reduced egg production observed in birds challenged with velogenic NDV genotype VIId was attributed to the excessive release of inflammatory cytokines, chemokines, lymphocyte infiltration, apoptosis, and severe pathological lesions in the oviduct of egg-laying hens [47]. The severity of infection of NDV in bursa of Fabricius was likened to the level of induction of pro-inflammatory cytokines, chemokines, apoptosis, macrophage infiltrations and oxidative stress (as a result of lipid peroxidation caused by nitric oxide released by macrophages). Oxidative injury and tissue damage caused by reactive oxygen and nitrogen species in NDV-infected cells is as a result of influx of phagocytic cells and release of pro-inflammatory cytokines in infection sites made worse by nutritional deficiency [48]. The severity of the pathological condition caused by NDV in infected hosts also depends on the NDV strain and is often marked with depletion in IgM+, infiltration of macrophages, the release of NOs (oxidative stress), infiltration of pro-inflammatory cytokines, chemokines and subsequently apoptosis [49]. Excessive production of IL-1β magnifies the inflammatory storm in NDV-infected hosts. NDV activates the oligomerization-domain leucine-rich repeats containing the pyrin domain 3 (NLRP3) inflammasome and caspase-1 cleavage in infected cells inducing the production and maturation of IL-1β, which magnifies the inflammatory damage in the host [50]. One of the studies reported that viral RNA alone is capable of inducing high amounts of IL-1β [51]. According to Li et al. [52], sphingosine-1-phosphate-1 receptor (S1PR1) overexpression also causes increased virus-induced IL-1β and excessive production of pro-inflammatory cytokines. Therefore, an appropriate amount of IL-1β is required to reduce viral replication as excessive amounts may induce inflammatory responses and/or lesions. Moreover, NDV trigger apoptosis in infected cells by upregulating the unfolding protein response (UPR) signaling (PERK-eIF2α, ATF6, and IRE1α), reduce anti-apoptotic genes and activate pro-apoptotic and inflammatory response proteins [53]. ISG12, an interferon-stimulated gene in chickens also stimulates apoptosis in NDV-infected cells to limit viral replication [54]. Necrosis and breakdown of collagen in the spleen of infected birds was as a result of the disruption of the extracellular matrix molecular composition/integrity and the upregulation of matrix metalloproteinase (MMP)-13 and 14 in NDV-infected cells [55].

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