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# Control and Prevention of Infectious Bursal Disease

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**Abstract:** Infectious Bursal Disease (IBD) is an acute, highly contagious, immunosuppressive viral disease of young chickens; IBDV predominantly targets B-cells residicing in the bursa of Fabricius (BF) and results in bursal edema, atrophy, and abrogation of antibody responses. Significantly, IBD-induced immunosuppression increases the occurrences of other diseases caused by opportunistic pathogens and, thus, prevents young chickens from responding optimally to vaccines. Owing to its widespread nature, high morbidity and mortality rates, IBD has been given a considerable economic importance both at the international and national levels and is of growing scientific interest. Most of the economic losses associated with IBD are due to its immunosuppressive effects that eventually lead to poor vaccination response, secondary bacterial, viral and protozoan infections and poor performance. The disease is mainly controlled by rigorous sanitary measures and vaccination through the use of either live or killed vaccines.

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## 1. Introduction

Infectious bursal disease (IBD), caused by a highly immunosuppressive virus, characteristically replicates in the lymphoid organs and directly suppresses the functionality of the immune system **(Zhai et al., 2014).** Infectious bursal disease virus (IBDV) is a double-stranded RNA virus, belonging to the genus Avibirnavirus within the family Birnaviridae **(Müller et al., 1979; Mahgoub et al., 2012; Ndashe et al., 2016)**. An Immunosuppressive viral agent like the IBDV is one of the factors that affect the protection level obtained to poultry from vaccination in the field. Hence, "sterilizing immunity" is not feasible in the field. IBDV is the etiological agent of "Gumboro disease", infecting chickens, leading to lymphoid depletion, and ends by destruction of the bursa, and subsequently, reduces the chicken's immune response to vaccination **(Müller et al., 2003; Swayne, 2006).** Vaccination of chickens against IBDV is mandatory and is a common practice in Egypt, where virulent and variant strains of the virus initiate mortality and immunosuppression leading to economic losses. However, the conventional whole attenuated IBD vaccines, which used in field carries the possible risk of bursal atrophy and immunosuppression **(Pradhan et al., 2012).**

**Control and Prevention of Infectious Bursal Disease**

**1-Exclusion or Eradication**

IBDV is very resistance to the physical and chemical agents **(Louzis et al., 1979))**. Its persistence in the environment, even after Disinfection, makes the eradication in the affected countries seems unrealistic **(van den Berg et al., 2000).** VTo prevent IBD **(Maris, 1986)** proposed several precautions such as practicing "all-in/all-out" farming methods; cleaning and disinfecting premises; and having a period of rest between depopulation and restocking **(Maris.1986).** The use of 10% hydrogen peroxide as the microaerosol mist can inactivate IBDV particles **(Neighbor et al., 1994)**; which is worthwhile to consider in the planning of the cleaning regime. In addition, several guidelines on the cleaning or disinfecting the IBDV contaminated farm premises had been described: Before cleaning, all insects and pests (for example rats and mice) need to be eliminated. After removing and decomposing the old bedding and dung, all farm equipment's are disassembled and relocated into a cleaning room outside the farm buildings. First, farm buildings are dry-cleaned. This is followed by washing with hot water (60 $^{o}$C) and detergent at a pressure of 80 to 150 bars. The concentration of the disinfectants should be about 4 litres per 15m2 **(Meroz and Samberg, 1995)**. And before introducing the new chicks, second disinfection of the full premises is warranted. The feed that remained from the previous flocks must never be reused **(van den Berg et al., 2000)**.

**2-Genetic Selection for Resistance**

The susceptibility of the host to various poultry pathogens depends mainly on its genetic makeup **(Yunis et al., 2002).** Resistance to IBDV infection could be breed-dependent, and crosses between resistant and susceptible lines had indicated the Resistance is a dominant hereditary phenotype **(van den Berg et al., 2000)**. Light breeds of chickens may have higher mortality rates than the heavier breeds **(Bumstead et al., 1993),** but inoculating IBDV in other avian species failed to cause the disease **(McFerran.1993).** Unfortunately, the genes that confer the resistance against IBDV are yet identified and it is not a common practice to selectively breed the resistance lines **(Bumstead et al., 1993**).

**3- Vaccinations**

Vaccination is the principal method of controlling viral disease in commercial poultry worldwide **(Lasher and Shane, 1994),** but never the substitute for good animal husbandry and hygiene practices. The success of vaccination depends on the choice of Vaccine strain, vaccination schedule, and the strains of the field isolate **(van den Berg et al., 2000)**. In the field, outbreaks of IBD have been controlled by vaccination practices **(Fussell, 1998).** The assorted IBDV strains with diversified antigenicity **(Jackwood and, Saif 1987)** (have complicated the vaccination programmes. Take, for Instance, the inactivated vaccines prepared from the vvIBDV strain may protect against the classical strain (STC isolate) but provided no protection against the variant strain (IN isolate) **(Abdel-Alim and, Saif,. 2001.).** In addition, antibodies against serotype 2 strain do not protect the birds from a virulent serotype 1 challenge **(Jackwood et al., 1985).** Therefore, vaccination against an IBDV strain may not protect the chickens against other strains challenges. Several types of IBD vaccines are available, namely the live, inactivated, and recombinant vaccines. Generally, recombinant vaccines may consist of the IBDV antigenic proteins (usually VP2) that had been expressed in different expression systems. DNA vaccine, on the other hand, may contain the genetic sequence (one or more genes) of IBDV. In practice, the attenuated live virus and oil-emulsion inactivated virus vaccines are used. The general principles regarding the choice and use of the IBD vaccines remained valid **(van den Berg et al., 2000).** And the standard requirements for preparing IBD vaccine were also described **(Thornton, 1976);** however, these requirements may be too idealistic and difficult, if not impossible, to achieve. In vitro antigen quantification had been reported as an alternative potency assay to measure the efficacy of IBD The ideal vaccine must not cause the disease or bursal lesions, must not be immunosuppressive or excreted, and must confer long-lasting immunity even in the birds that have high maternal immunity. Unfortunately, such ideal vaccine is yet to be found **(McFerrin, 1993)**. Early vaccination at 7 days was reported to be superior to vaccination the birds at 14 or 28 days for better antibody response and protection against mortality and bursal lesions **(Adene et al., 1989).** Chickens vaccinated with IBDV in early life and revaccinated with an inactivated, oil-adjuvant IBD vaccine at 18 weeks of age produced and maintained high levels of virus-neutralizing antibody through 10 months of lay **(Naqi et al., 1983)**. The route of vaccination, such as oral followed by parenteral administrations of IBDV antigen had been reported to induce an enhanced antibody response in chickens **(Hoshi et al., 1995).**

**3.1 Live Virus Vaccines**

Live virus vaccines are generally derived from the serial passages in embrocated eggs **(van den Berg et al.,2000)** In general, the live IBDV vaccines in use by the poultry industry have been attenuated by serial passage in tissue culture, eggs or embryo-derived tissues, with the aim of maintaining the immune response induced by the parent virus whilst attenuating the ability of the vaccine virus to cause clinical disease or significant immunosuppression **(Schijns et al., 2008)** The degree of attenuation of the vaccine strains can be classified as mild, intermediate, and hot; depending on its ability to cause the varying degree of histological lesions **(OIE, 2000).** Although serotype 1 vaccine strains cause no mortality, it still causes different degrees of bursal lesions that range from mild to moderate or even severe **(van den Berg et al.,2000).** The higher the virulence of the vaccine virus strain, the more severe damage of the bursal lymphocytes resulted **(Kelemen et al., 2000).** Nonetheless, as it should be, the lesion caused by the vaccine strain is less severe than the field strain **(Rosales et al 1989)** mild strain is mainly used in the breeder vaccination programme. Given the mild strain subjects to the maternal antibody interference, it is therefore usually used between the fourth and eight week of age, depending on whether the grandparent birds have or have not been vaccinated with oil-emulsion inactivated vaccine before lay **(van den Berg et al., 2000).** Intermediate vaccines are used for broiler and pullet vaccination **(Mazariegos et al., 1990),** and sometimes to breeder chicks when the flocks are at risk of early challenge of highly pathogenic strains. Day-old vaccination using intermediate vaccine may protect the chicks that have insufficient maternal antibody **(van den Berg et al., 2000).** Besides, early vaccination will spread the vaccine virus in the farm premises and provides indirect vaccination to the other susceptible chicks **(van den Berg et al., 2000).** In high-risks farms, two vaccinations are generally practice. The time of

vaccination depends on the flocks' maternal antibody titres. Route of vaccination is usually through drinking water, although nebulisation could also be used **(van den Berg et al., 2000.)** To achieve higher maternal antibody in the progeny, vaccination of broiler breeders with live IBD vaccine by the oral route is better than the intramuscular injection **(Wyeth et al., 1981).** Meanwhile, vaccination of parent chickens with a commercial live IBD vaccine under field conditions at varying ages and by different routes may result in the variable susceptibility to the disease in their chicks **(Wyeth and Cullen, 1978).** *In ovo* vaccination with a mixture of vaccines against IBD and Marek's disease protects the hatched chicks against both diseases **(Sharma and. Embryo, 1985)** Embryoithout inhibiting individual viral agents on humoral and cellular immune competence **(Gagic et al., 1989).** Moreover the use of a multivalent *in ovo* vaccine (comprised of IBDV, Marek's disease virus, and a recombinant fowl poxvirus vector that contained HN and F genes of Newcastle disease virus (ND)) was reported successful in field conditions **(Sharma et al.,2002).** *In ovo* vaccination using IBDV alone could resisted the challenges with pathogenic IBDV at 4, 6, 8, and 10 weeks of age **(Sharma et al., 1986).** Notwithstanding with the above findings, other scientists reported that although *in ovo* IBD vaccination may protect SPF chickens from IBDV challenge, the protection in commercial chickens was incomplete after the challenge - evidence by the presence of bursal lesions **(Coletti et al.,2001).** *In ovo* vaccination may also reduce the immune response to ND vaccination in SPF chickens, but similar phenomenon was not observed in commercial chickens **(Coletti et al.,2001).** Other found that *in ovo* vaccines may cause significant microscopic lesions in the bursa of Fabricius at 1 and 3 wk posthatch **(Giambrone et al.,2001).** *In ovo* vaccination with "antibody-mixed live vaccine" provides an alternative mean of vaccination, in which this practice may avoid the interference from the maternal antibodies and protect the chickens against IBD **(Haddad et al., 1997). Whitfill *et al*. (1995**) developed this type of IBD vaccine by mixing the anti-IBDV antibody with the virus particles itself **(Whitfill et al., 1991,)** (referred as "antibody-mixed live vaccine"). The vaccine was administered through *in ovo* route to the SPF embryos and was reported to be safer and more potent than the conventional IBD vaccine because it delayed the appearance of bursal lesions, produced higher geometric mean antibody titers against IBDV, generated protective immunity against challenge, and produced no early mortality **(Johnston et al., 1997).** The working mechanism of "antibody-mixed live vaccine" was thought to be related to its specific cellular interaction with the follicular dendritic cells in spleen and bursa **(Jeurissen et al., 1998).** The disadvantages of *in ovo* vaccination using "antibody-mixed live vaccine" might be the transient bursal destruction, observed both in SPF and commercial broilers **(Ivan et al., 2001).** Some reported the vaccine may cause bursal atrophy **(Corley et al., 2001)** and cell-mediated immunosuppression **(Corley et al., 2002).** The "antibody-mixed live vaccine" had been given various names and may lead to confusion, these names were: "IBDV–bursal disease antibody (IBDV-BDA) vaccine" **(Ivan et al., 2001)** "BDA-IBDV" **(Johnston et al., 1997),** "IBDV immune complex vaccine (ICX)" **(Corley et al., 2001),** "*in ovo* complex vaccine" **(Kelemen et al., 2000)** and "antibody-coated IBDV vaccine **(. Kumar.2001).**

**3.2 Inactivated Vaccines**

Inactivated vaccines are usually used in the breeder hens for them to pass down high, uniform, and persistent antibody titres to the progeny **(Guittet et al., 1992)** for the vaccination to be effective, the hens must be previously vaccinated with a live virus or had been exposed to the virus in the farm. Inactivated vaccines are administered to the layers through subcutaneous or the intramuscular route at sixteen- to twenty-week-old. In this way, the chicks will have the protective maternal antibodies up to thirty days **(Wyeth and Chettle, 1992)**. Inactivated vaccine is usually prepared from the bursal homogenates of infected chickens or from viral cultures on embryonated eggs or fibroblast cells; where the virus is then Inactivated by formaldehyde and various alkylating agents like binaryethylenimine (BEL) and betapropiolactone and prepared as the oil emulsions **(van den Berg et al., 2000).** Physical means such as high hydrostatic pressure can also produce inactivated vaccine by dissociating the virus particles into subunits while preserving its immunogenicity **(Tian et al., 2000).**

**3.3 Recombinant and DNA Vaccines**

Infectious bursal disease virus proteins expressed in other prokaryotic systems can serve as IBD recombinant vaccine. The recombinant IBDV protein will be a more effective vaccine if it precisely mimics the authentic molecular structure of the viral protein **(Martinez-Torrecuadrada et al., 2003)**. Structural proteins of IBDV had been expressed in the baculovirus expression system. The baculovirus-expressed protein induces immunological response **(Wang et al., 2000)** and protects the chickens from IBDV challenge **(Pitcovski et al., 1996)** However; the protection is incomplete, evidence by the presence of bursal damage after IBDV challenge **(Dybing and Jackwood, 1998)**. In comparison with virus-like particles (VLP), VPX tubules, and polyprotein-derived mix structures, the baculovirus expressed VP2 capsids elicit stronger immune response **(Martinez-**

**Torrecuadrada et al.,2003)** Improved technology for producing recombinant IBDV protein using baculovirus expression system had also been documented **(Wang and Doong,2000)**. Reports indicated that VP2 had also been expressed in other expression vectors such as the herpesvirus **(Tsukamoto et al.,2002)**, Marek's disease virus **(Tsukamoto et al.,2000)** fowl adenovirus **(Sheppard *et al*., 1998)**, fowl pox virus **(Heine and Boye,1993),** and Semliki Forest virus **(Sheppard et al.,1998);** in which they may serve as recombinant IBD vaccines. Recombinant fowl pox vaccine protects the chickens from the IBDV-induced bursal damage but its efficacy depends on the titre of the challenge virus and the chicken genotype **(Phenix et al., 2001)**. In addition, the effective application of recombinant fowl pox (VP2) vaccine may be restricted to the wing web and parenteral routes of inoculation **(Shaw and Davison, 2000)**. In eukaryotic expression system, VP2 expressed in the yeast confer passive protection against IBD **(Boyle and Heine, 1994)**; probably because the multimeric forms yeast-derived VP2 were highly immunogenic, expressions of VP2 in *E. coli* are not immunogenic **(Macreadie et al., 1990)**. Aside from single type of recombinant vaccine, the dual-viral vector approach — an approach that uses Marek's disease and Fowl pox viruses that express vvIBDV host-protective antigen may serve as a quick and safe method in inducing strong and long-lasting protective immunity against vvIBDV **(Tesfaheywet et al.,2012)**. Deoxyribonucleic Acid vaccine could provide efficacious protection for chickens against IBDV infection (Azad et al., 1991). Effective DNA vaccine included the VP2 gene in the plasmid DNA (Chang et al., 2001). Transcutaneous plasmid-dimethylsulfoxide (DMSO) delivery technique for avian nucleic acid immunization had been described **(Chang et al., 2003).** It was pointed out that DMSO enhances liposome-mediated transfection of nucleic acid in chicken macrophage cells and this phenomenon was exploited for the transcutaneous delivery of naked DNA through the intact skin of the chickens. DNA-based IBD vaccine had been delivered using this technique and the chickens were protected against IBD (86% survival) **(Chang et al., 2003).** Recombinant vaccines offer several advantages over other types of vaccines such as the absence of residual pathogenicity, low sensitivity to maternal antibodies, low risk of selection of mutants, the possibility to administered through *in ovo* route, and may enable one to distinguish between the infected and vaccinated animals **(Heckert et al., 2002)** Although these vaccines are said to be available in the market **(Meeusen et al., 2007).**

**4. Anti-viral Drugs**

Apart from producing the myriad types of IBD vaccines, other scientists are in search of alternative ways to fight against the disease. For example, by feeding *Azadirachta indica* (Neem) dry leaves powder to the IBDV-infected birds, scientist found the bird's humoral and cell-mediated immune response were improved **(Chettle et al.,1989).** Supplementation of ascorbic acid at 1,000 ppm in the diet is beneficial to the chickens that are vaccinated against IBD **(Sadekar et al., 1998)**. This is probably because ascorbic acid has ameliorated the immunosuppression caused by IBDV vaccination and thus improved the humoral and cellular immune responses of the vaccinated birds **(Amakye-Anim et al., 2000).** Moreover, ascorbic acid supplemented birds have higher body weight gains in comparison with the non-supplemented group **(Sadekar et al., 1998).** Other suggested that feeding crude thymus extract to the IBD-vaccinated chicks may improve the vaccination effectiveness because this practice could improve the body weight gain and conferred better protection against IBDV challenge **(Wu et al., 2000).** Virus neutralization factor (VNF) is a class of non-specific antiviral agents produced in vivo in chickens in response to viral infection and can directly inactivate the IBDV particles **(Abdel-Fattah et al., 1999)** meanwhile, inoculating concentrated anti-IBDV immunoglobulin extracted from the egg yolk into SPF embryonated eggs may produce chicks with passive immunity and protected against IBD **(Whitfill et al., 1991).** The recombinant interferon alpha, which has antiviral effect, has shown to suppressed IBDV plaque formation in a dose-dependent manner and ameliorated IBDV and ND virus infection in both SPF and commercial chickens **(Eterradossi et al., 1997).** The effect of the interferon therapy, while depending on the route of administration, is more obvious in commercial chickens than in SPF chickens **(Eterradossi et al., 1997).**

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