AviPod
An Update for Poultry Professionals
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Immunomodulation and Disease Prevention in Poultry

Immunity plays a crucial role in poultry farming. Growth, disease resistance, feed conversion ratio (FCR) and body weight gain all depend directly and indirectly on immunity of the bird. Hence, it affects profit of the farmer and health of consumer. In poultry nutrition and health, a basic understanding of immune system is a must requirement. Immunity provides protection against disease and is mediated by a collection of molecules, cells, and tissues collectively called immune system.

Birds respond to antigenic stimulation by generating antibodies as well as cellular immunity. Birds raised under commercial conditions are vulnerable for exposure to number of pathogens. Immune system initiates and manages appropriate physiological responses to neutralise and/or eliminate these pathogens. A strong immune system protects birds from infections.

Modulation of immune system denotes any change in immune response that can involve induction, expression, amplification or inhibition of any part or phase of immune response. Thus, an immunomodulator is a substance that stimulates or suppresses the immune system..

Organs of immune system in poultry are

- Bursa of Fabricius
- Thymus
- Spleen
- Bone marrow
- Lymphoid cell aggregates along gut, trachea, oesophagus, Harderian gland and cecal tonsils
- Circulating lymphocytes

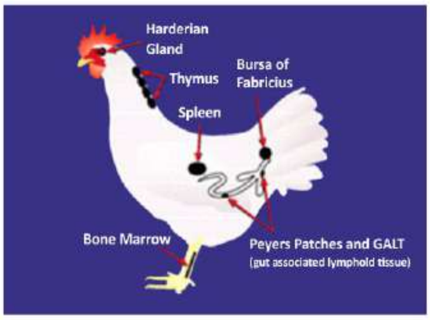

Fig. 1: Immune organs in poultry

Avian immune system is different from mammalian immune system.

Two features of avian immune system are:

- Birds lack highly organised lymph nodes as in mammals. However, rudimentary lymph nodes develop in lymphatics but do not interrupt lymph flow. They are located in the wall of deep lymphatics and are therefore referred as 'mural lymph nodes'.
- Second significant difference is presence of a unique lymphoid organ, bursa of Fabricius (BF), only found in birds. It is the site of B-cell development. Interestingly, bursa involutes at sexual maturity.
- Other structural and functional differences between birds and mammals are reduced numbers of cytokines as well as chemokines and morphological difference of germinal centres.

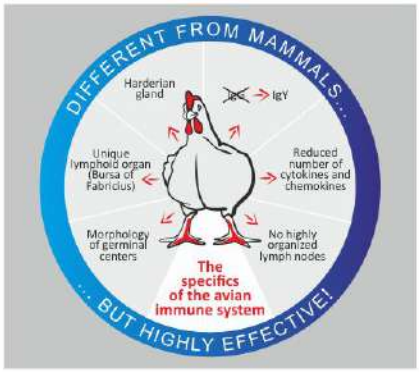

Fig. 2: Specifics of avian immune system

Nevertheless, birds achieve the same response to pathogenic challenges as mammals. Birds mount highly effective adaptive immune responses to infection or vaccination compare to mammals. Germinal centres are formed in mucosa-associated lymphoid tissues (e.g. Harderian gland, bronchus-associated lymphoid tissue, cecal tonsils) and spleen in response to immunisation, leading to formation of high-affinity antibodies and class switching from IgM to IgY (IgG) immunoglobulins. These structures compensate for the lack of lymph nodes.

Avian immune system is broadly divided into:

- Innate/non-specific and
- Adaptive/specific immune mechanisms

These work together to recognise and protect against disease-causing agents, including pathogenic bacteria, viruses and fungi.

Innate / Non-Specific Immunity

Innate immunity is bird's **first line of immune defence** against a wide variety of pathogens. It includes inherent ways in which chicken resists disease. Responses of innate immune system are 'non-specific' and do not distinguish between invaders but respond to features that are common to many types of pathogens. Innate immune system has several components that help to provide the initial defense response. These are physical and chemical barriers, blood proteins and cellular components.

- **Physical and chemical barriers** include skin, mucosal epithelium, and secretions of gastric and respiratory tracts that help against possible infection. Many infectious organisms cannot penetrate intact body coverings or are trapped in the mucus secretions. Some nutritional deficiencies or infectious diseases compromise the integrity of body coverings, allowing penetration of disease organisms.

  Normal microflora: Skin and gut normally maintain a dense stable microbial population. This stable microflora prevents invading infectious organisms from gaining a foothold. Improper use of antibiotics or poor sanitation can disrupt the balance of microflora.

  Poultry gut immunity: Gastrointestinal (GI) tract is an important organ for maintaining health. Besides digestion and nutrient absorption, it acts as barrier against unwanted compounds and germs. Because of its extensive surface, GI tract is also a major port of entry for many pathogens. Immune system of GI tract has a major responsibility to act on known pathogens while ignoring components of food or 'commensal' microorganisms that inhabit the gut. Failure to do this might end in intestinal inflammation and tissue degeneration.

  Respiratory tract cilia: Parts of respiratory system are lined with cilia, which remove disease organisms and debris. If air in poultry house is of poor quality due to high levels of dust or ammonia, the ciliary system may be overwhelmed and become ineffective.

- **Blood proteins:** One specific blood protein called 'complement' is a serum protein that works in conjunction with antibodies to help identify certain target cells that ultimately lead to their destruction.
- **Cellular components** of innate immune system include:
  - Macrophages
  - Natural killer (NK) cells
  - Heterophils
  - Thrombocytes
  - Eosinophils
  - Basophils

Many of these innate protector cells, such as macrophages have a phagocytic role, ingesting and eliminating pathogenic microbes. A microbe's pathogenicity refers to its ability to resist the innate immune system. When this non-specific immune response cannot cope with the pathogen, then adaptive immune system begins to respond.

High body temperature of chicken also precludes many diseases. Body temperature of poultry ranges between 40.5-41.5°C/ 105-107°F, which prevents a number of common mammalian disease organisms from affecting birds.

One of the most common signs of activation of innate immune system is **inflammation**, which serves to protect against the initial cause of body cell injury. It removes necrotic cells and cells damaged by the injury and the inflammatory process and initiates tissue repair.

Adaptive/ Specific Immunity

- Adaptive immune system takes a more targeted approach as it recognises specific features on the surface of pathogen, thus beginning a cascade of events leading to elimination of pathogen and creation of **'memory'** that provides protection from future exposure to that same pathogen.

- Adaptive immunity makes use of lymphocytes – white blood cells capable of recognising antigens. Lymphocytes include B-cells and T-cells, which initiate a series of events ending with elimination of the antigen. In birds and mammals, thymus is a primary lymphoid organ where maturation of T-cells occurs. However, unique to avian species, maturation of B-cells takes place in the bursa of Fabricius.

Specific immune mechanisms are characterized by specificity, heterogeneity and memory. Specific types of lymphocytes recognise and eliminate invading pathogens. This system is divided into

- Humoral (Non-cellular)
- Cell-mediated immunity

Humoral Immunity

Humoral component includes immunoglobulins (antibodies). Antibodies are specific for the foreign material (antigen) to which they attach. In poultry, 3 types of antibodies are produced after exposure to a disease organism: IgM, IgG or IgY and IgA.

- **IgM** appears after 4 - 5 days following exposure to a pathogenic organism and then disappears by 10 - 12 days.
- **IgG** or **IgY** is detected after 5 days following exposure, peaks at 3 - 3½ weeks and then slowly decreases. It is important protective antibody in chicken and is measured by most serological test systems.
- **IgA** appears after 5 days following exposure. It is found primarily in the mucus secretions of eyes, gut, and respiratory tract and provides 'local' protection to these tissues.

The cells which produce antibodies are called B-lymphocytes. These cells are produced in embryonic liver, yolk sac and bone marrow. The cells move to the bursa of Fabricius after 15 days of incubation to 10 weeks of age. Bursa of Fabricius programs these cells, which then move to blood, spleen, cecal tonsils, bone marrow, Harderian gland and thymus. Destruction of bursa of Fabricius at a young age by Gumboro disease or Marek's disease prevents programming of B-cells. In this case, chicken will not be able to respond to diseases or vaccinations by producing antibodies.

When a disease organism enters in body, it is engulfed by macrophage. Macrophage transports the organism and exposes it to B-lymphocytes. B-cells respond by producing antibodies after day 5 following exposure. The lag period occurs because the B-cells must be programmed and undergo clonal expansion to increase their numbers. If the chicken is exposed a second time to same disease, the response is quicker and a much higher level of antibody production occurs (memory). This is the basis for vaccinating.

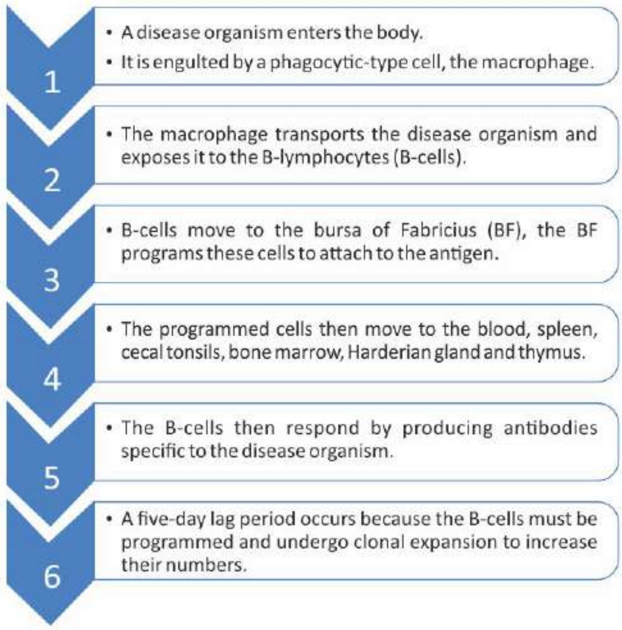

Fig. 3: Development of humoral immunity

Antibodies perform their function by attaching to infectious organisms and blocking their receptors. The disease organisms are then prevented from attaching to their target cell receptors in the chicken. The attached antibodies also immobilize the pathogenic organism, which facilitates their destruction by macrophages.

Cell-Mediated Immunity

- It involves T-lymphocytes and is the primary defence mechanism for elimination of pathogens that manage to invade body cells and so are not accessible by circulating immunoglobulins of humoral response. T-lymphocytes are programmed in thymus.
- T-cells of cell-mediated response can be broadly divided into CD4+ **'helper'** T-cells and CD8+ **'cytotoxic'** T-cells. These T-cells only recognise peptide antigens that are present on the surface of invading pathogens.
- In response to presence of pathogenic microbes and their antigens, recognition helper T-cells secrete cytokines, which mediate and regulate various mechanisms of both innate and adaptive immune systems, including inflammation, macrophage activation (innate) and activation, proliferation and differentiation of T-cells and B-cells (adaptive).

- Cellular system was identified when it was shown that chickens with damaged bursa of Fabricius could still respond to eliminate many disease organisms.

In adaptive immune response, once activated by antigen recognition, cytotoxic T-cells break down the infected cell. After exposure to an antigen, B-lymphocytes and T-lymphocytes can further differentiate into 'effector' and 'memory' lymphocytes, which represents 'learning' in adaptive immune system. If immune system of bird encounters the same pathogen again, then these lymphocytes can quickly identify the pathogen and eliminate it. Vaccination makes use of 'learned' adaptive immune response to provide protection against pathogens that the bird has not yet encountered.

A chicken may become immune to an infectious organism by producing antibodies itself or by obtaining pre-made antibodies. When chicken produces its own antibodies following exposure to foreign material, the process is called **active immunity.** This occurs when bird is exposed to a vaccine or a field disease challenge. Active immunity is harmed by anything, which damages cellular or humoral immune systems.

When chick receives pre-made antibodies from the hen through egg, this is termed as **passive immunity**. Maternal antibodies are present in yolk, albumin and fluids of the egg. If hen has a high antibody titre level to a disease, the chick should also be immune for several weeks. Since, immune system of the chick is not stimulated, no antibodies and memory cells will be produced by the chick. If chickens are vaccinated when maternal antibody titre levels are elevated, the vaccine may be buffered excessively resulting in a reduced response.

In summary, immune system of chicken is very helpful in preventing disease and helping to ensure maximum productive potential. Many factors can impact the performance of avian immune system, which is critical to poultry health and productivity.

Factors Affecting Bird Immunity and Their Control

- **Stress:** Immunosuppression in poultry is mainly caused by stress which may be by managemental, environmental (heat/cold), improper biosecurity, nutritional or any disease condition. Sudden change in managemental practices like feeding, watering, temperature, very high or low humidity causes stress to the birds. Stress increases production of corticosterone, ultimately leading to depletion of lymphoid organs. Stressed birds may fall short to perform with respect to body weight, feed efficiency, laying performance and mortality. This causes potential economic losses.

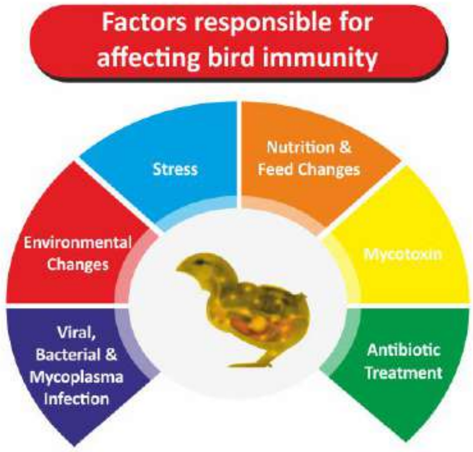

Fig. 4: Factors affecting bird immunity

- **Nutrition:** Well-nourished birds are immunologically more competent and have more resistance to diseases. Poor nutrition lead to deficiencies, which allow pathogenic organisms to penetrate the protective body coverings. There are many vitamins (e.g. Vitamin E), minerals (e.g. Selenium) and amino acids whose deficiency in poultry feed cause immunosuppression. Free radicals or oxidative compounds can be ingested through poorly stabilized fats, oils and animal by-products, which are able to damage cell membranes. Vitamin E is able to remove these oxidative molecules. Hence, deficiency of it causes increase in number of free radicals, which indirectly suppress immune system. Certain nutritional interventions can positively affect immune function.

- **Infectious diseases:** Almost all diseases of poultry can suppress immune system; however, certain diseases whose virus replicates in immune organs like bursa/ thymus, directly influence immune system. These include infectious bursal disease (IBD), chicken infectious anaemia, Marek's disease, reovirus infection, Newcastle disease and avian influenza.

  To control these infections, appropriate vaccination schedule should be adopted for breeders so that their chicks can have appropriate maternal antibody levels against these diseases.

Fig. 5: Enlarged yellow greyish bursa of Fabricius (right) & hemorrhagic bursa (left) in IBD affected bird

- **Mycotoxins:** Mycotoxins are the metabolites of fungi commonly called molds. Molds grow and produce toxins in grains and other poultry feed ingredients during growing, harvesting or storage of crop. Aspergillus,

- Penicillium, and Fusarium are the fungi whose metabolites mainly affect poultry feed ingredients. Major ingredients on which these fungi may grow are maize, wheat, rice and peanut meal.
  - ➢ Aspergillus produces aflatoxin, which impairs immune cells functioning. Aflatoxin is also responsible for lymphoid depletion and necrosis in bursa of Fabricius, spleen & thymus and hepatotoxicity.
  - ➢ Penicillium produces ochratoxin A, which is associated with generalized impaired humoral and cell mediated immune responses. It is also nephrotoxic.
  - ➢ Fusarium produces trichothecene, which suppresses immune system in two ways, firstly, it is a strong tissue irritant and alters mucosal membrane integrity. Secondly, it inhibits protein synthesis and consequently interferes with antibody production.

Consequences of Immune Deficiency in Poultry

- Disease outbreak: Birds with immunodeficiency are more likely to get sick due to
  - ➢ Insufficient innate immune response
  - ➢ Lower antibody titre after vaccination or vaccine failure
  - ➢ Increased secondary infections
  - ➢ Sensitization: fewer microorganisms needed to cause disease

Fig. 6: Consequences of immune deficiency

- Increased mortality.
- Increased FCR, poor performance, impaired growth, less uniformity of the flock and carcass condemnation.
- Thus, immunosuppression causes poor production and economic losses, which necessitate its prevention for better flock health, vaccination response, performance and uniformity of flock. This can be achieved by controlling infectious diseases, providing good management, maintaining appropriate environment and by good nutrition.

Optimising Immune Function

- A number of naturally occurring viruses cause immunosuppression in chickens. There is much current interest in understanding the mechanisms of immunosuppression and developing strategies to enhance immune responsiveness in commercial poultry.
- In poultry, successful defence against invading pathogens requires a coordinated effort between both innate and adaptive immune responses and their various components. Much more research is underway to understand how natural products delivered through feed or water can support the optimal and efficient functioning of bird's immune system. Specific influences investigated include effects on innate immunity through natural killer cell activity, complement and lysozyme activity.

Immunomodulators

- Immunomodulators are either natural or synthetic substances, which specifically modulate immune system regulating immunity and disease resistance. They are also called as **biological response modifiers** (BRMs). In poultry, it is specifically important as growth, disease resistance, FCR, body weight gain and production output mainly depends on health and immunity of the chickens.
- Immunomodulators modify and optimally control immune responses of body, modifying disease resistance, vaccine and antibiotic efficacy and improving digestive tract microflora. Nowadays, microbes are increasing resistance against antibiotics; hence, immunomodulation can be a virtuous alternative prophylactic and therapy. They act on immune system and its molecules (not on the microbes directly), along with broad spectrum ability.

Objective of Immunomodulation

- Preliminary objective of immunomodulation is to improve host resistance to external and internal attacks by microbes or other infectious agents.
- Augmentation of immune response is desirable to prevent infection in states of immunodeficiency, to fight established infections.
- To enhance duration and level of immune response following vaccination.
- Immunomodulators can substitute many agents like antibiotics, antimicrobials etc. for improvement of the immune system.

As immune system is directly related to disease resistance, gut health, FCR, etc., hence immunomodulators must be used in combination and/or alone according to needs. They also enhance qualities of feed and immune molecules enhancing all possibilities to fight diseases and maintain health homeostasis. There has been an increased interest in the use of immunomodulators as substitutes for antibiotics in poultry production.

Commonly used immunomodulators in poultry

Essential oils

Vitamins and minerals

Prebiotics

Probiotics and

Next generation immunity booster

- Beta Glucans and
- Nucleotides

Essential oils

- Essential oils from tulsi, ashwagandha, garlic, turmeric and aamla have been found to be beneficial in summer season to reduce heat stress in layers.
- Aamla and ashwagandha are also helpful in broilers for improving immune status and body weight. They act as an antioxidant.

Vitamins and Minerals

- They play important role in protecting against oxidative damage. Free radicals are scavenged by Vitamin E as a first line of defence. Hence, Vitamin E assist in the maintenance of membrane integrity.
- Vitamin E is a fat-soluble vitamin and its dietary intake reduces heat stress and improves egg production. Vitamin E shall be supplemented before, during and after any stressful condition.
- Selenium is an essential nutrient for poultry and is important for a number of physiological processes including regulation and function of the immune system. Through its incorporation into selenoproteins, Se is involved in regulation of oxidative stress and other crucial cellular processes involved in innate and adaptive immune response.

Prebiotics

- Prebiotics are non-digestible feed ingredients that are metabolized by specific members of intestinal microbiota and provide health benefits for the host.
- Prebiotics are capable of modulating gut microbiota and immune interactions in favour of chicken health.

Probiotics

- Probiotics are a combination of live beneficial bacteria and/or yeasts that naturally live in body. They have been used as prophylactic agents against enteric pathogens, presumably by balancing microbiota, by modulating host immunity or both. Dietary *B. subtilis*, when used in a broiler as a potential growth promoter, can provide beneficial effects on broiler performance and modulate host humoral and cellular immune responses to enteric pathogens.
- Regular and judicious use of probiotics has a striking effect on the immune system viz. stimulation of both humoral and cell mediated immunity through enhanced production of natural interferons/cytokines; increased macrophage, lymphocyte and natural killer (NK) cell activity; upregulated oxidative burst in heterophils; and increased immunoglobulin (IgG, IgM and IgA).
- Probiotics produce a gut-stabilising effect and good immune regulation, particularly through balanced control of pro-inflammatory and anti-inflammatory cytokines.
- Feeding probiotics could improve antibody titres against viral diseases like Newcastle disease (ND) and Infectious bursal disease (IBD).
- Use of probiotics increases amount of IgA found in intestinal lumen, numbers of IgA, IgM and IgG producing cells as well as number of T cells in the cecal tonsils.

Next Generation Immunity Booster

Beta-Glucans

β-Glucan is a water-soluble dietary fibre obtained from oats, barley, bacteria, yeast, algae, and mushrooms. Cell wall of baker's yeast *(Saccharomyces cerevisiae)* is most abundant in β-glucan. β-Glucan is a polysaccharide consists of glucose units. Glucose monomers are linked via β-(1→3) glycosidic bonds in bacteria and algae whereas via β-(1→3) and β-(1→6) glycosidic bonds in yeast and mushrooms. The role of β-glucans as biologically active immunomodulators in mammalian systems has been well documented. With the desire to find alternatives to antibiotics in poultry production, research looking at the effect of β-glucans on avian immune system has increased recently.

- β-glucans increase host immune defence by activating complement system, enhancing macrophages and natural killer cell function.
- Among β-glucans from microbial sources, those from the yeast *Saccharomyces cerevisiae* have been found to be most active. It is having highly branched structure (beta-1,3 and 1,6,glucan) and have been found to be the most effective types of β-glucans in terms of immune system stimulation.
- Studies have shown that (1→3)(1→6)-β-glucans can enhance the functional activity of macrophages as well as activate antimicrobial activity of mononuclear cells and neutrophils. Inclusion of purified yeast β-glucan was shown to stimulate phagocytosis, bactericidal killing and oxidative burst in chickens.

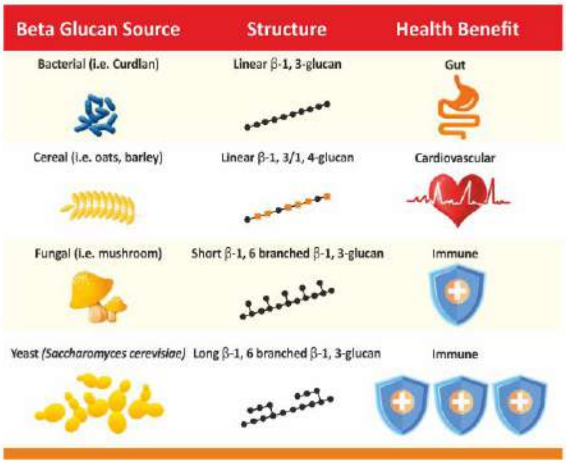

Fig. 7: Health benefits of β-glucans from different sources

- Broiler chickens fed diets supplemented with yeast β-glucan [a (1→3)(1→6)-β-glucan] had enhanced humoral and cell-mediated immune responses (Zhang *et al.*, 2008).
- In addition, immune-enhancing effects of (1→3)(1→6)-β-glucans have also been shown to be effective in preventing colonization by several economically important pathogens, including *Salmonella enterica* and *Escherichia coli* (Lawry *et al.*, 2005).
- Dietary levels of (1→3)(1→6)-β-glucan above 0.02% were shown to improve growth performance and nutrient retention in addition to improved immune function of broiler chickens.

Nucleotides

- Nucleotides are the building blocks of DNA and RNA and are necessary for any form of cell replication.
- It causes faster recovery after injuries or disease.
- It causes increased resistance to bacterial and viral infections.
- Dietary nucleotides have been reported to play a crucial role in immune system, such as lymphocyte activation (Carver and Walker, 1995).
- Dietary nucleotides play a beneficial role to defend against bacterial or fungal infection by increasing host resistance to such infection (Kulkarni *et al.*, 1986).

In certain situations such as diseases and stress, body may not produce enough nucleotides to maintain optimal function. Hence, supplementing diet with nucleotides is crucial.

General Benefits of Immunomodulators

- Improves immune status of birds
- Helps in faster recovery from disease
- Enhance overall health
- Improves gut health and reduces diarrhoea
- Improves feed intake and body weight gain
- Helps in relieving stress
- Improves egg production and hatchability
- Enhances the protection induced by vaccine by improving antibody titre

With the increased pressure to reduce antibiotic use in poultry production, producers are looking at boosting immune function as an alternative approach to reducing the effects of intestinal pathogens. β-glucans from fungi and yeast are ideal immunomodulators for poultry, since they enhance the immune system without affecting production performance. Commercially available **IMMUTAS PLUS** and **IMMUTAS WS** contains second generation immunomodulator β-glucans, Nucleotide and other immuno nutrients. According to various trial reports by poultry experts across India, it is found to be an effective immunomodulator in poultry. **IMMUTAS PLUS** can be added in feed at dose rate of 100-200 g/ton of feed or **IMMUTAS WS** in drinking water at dose rate of 100 ml/1000 birds.

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