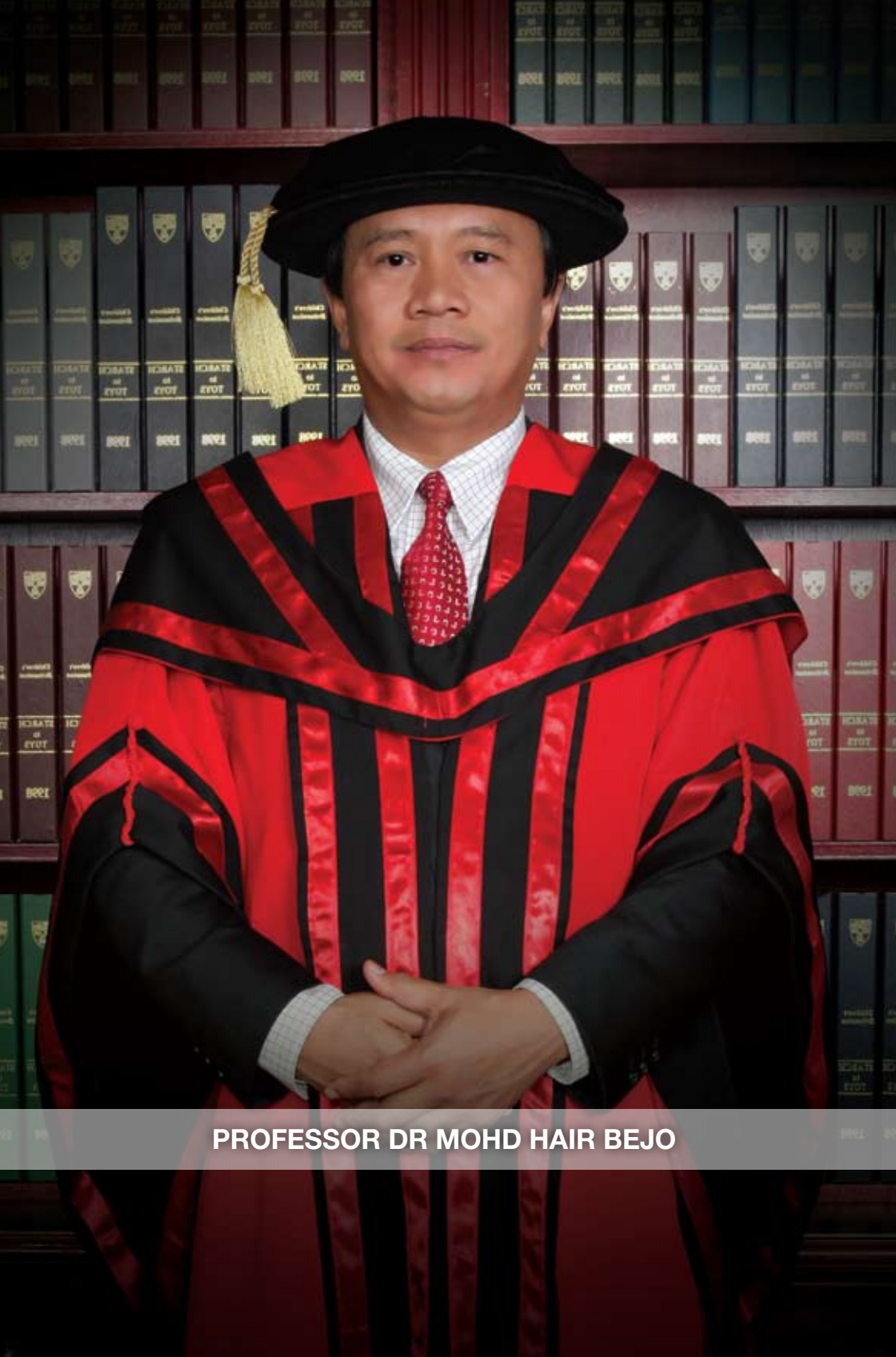
Poultry Vaccines
An Innovation For Food Safety & Security



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An Innovation For Food Safety & Security

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"Innovation is a process by which an idea or invention is translated into a good or service for which people will pay. To be called an innovation, an idea must be replicable at an economical cost and must satisfy a specific need"

(BusinessDictionary.com)

ABSTRACT

The poultry industry in Malaysia has played its role in contributing to the realization of agriculture as the third engine of growth and a high income economy, which is the goal of the new economic model (NEM) and food security. The industry has grown significantly at about 5.95% annually from 714,300 to 1.202 million metric tonnes from year 2000 to 2009, with total ex-farm value of RM5.468 billion or 53% of ex-farm value of the livestock industry. The total export of chicken products increased from RM54.44 million in 2007 to RM 350.68 million in 2009. In addition, 510 million metric tonnes of eggs was produced in 2009, with total ex-farm value of RM2.226 billion or 22% of ex-farm value of the livestock industry. The industry has contributed 86% of livestock production and 75% of the ex-farm value of the livestock industry in the country. Poultry products are a major source of protein which is relatively cheap, easily available and acceptable to most or a majority of the society in the country and worldwide: we feed the world. The industry is run commercially by large-scale integrators and multi-national corporations and is an example of a success story in the livestock industry in the country, and could perhaps act as model for the livestock industry. However, the industry is not free from many issues and challenges such as high production costs and emerging and reemerging diseases. To date, almost all known major poultry diseases have been reported in Malaysia. Thus, without proper management programmes and appropriate intervention the health and production of chickens, as well as the quality and safety of the products, can be badly affected. The success of chicken production depends to a significant degree on the flock health and prevention of diseases. Most problems related to disease in the chicken industry today are caused by the interaction of many factors where immunosuppression plays a key role and is a frequent problem in

chicken production. Control and prevention of poultry diseases involves complex understanding of the interaction of the agent, host and environment, and this can usually be achieved by proper biosecurity, vaccination and flock health programmes. It is difficult and expensive to maintain a high level of biosecurity at all times. Thus, poultry vaccines are powerful tools in disease control and prevention. Malaysia imports vaccines and pharmaceuticals worth RM 650 million annually and thus the Department of Veterinary Service is looking into ways of producing at least 30% of these vaccines locally. While there are 35 veterinary vaccine importers in Malaysia, Malaysian Vaccines and Pharmaceuticals Sdn Bhd (MVP) is currently the sole veterinary vaccines manufacturer in the country. MVP manufactures 10 poultry vaccines against 4 important poultry diseases, namely the NDV4, FP, IBD UPM93, IBD, NDF, NDS, NDB1, NDLasota, NDB1/H120 and NDLa/H120. Of these, 3 of the vaccines against 3 important poultry diseases, namely the NDV4, FP and IBD UPM93, are innovations from our research team at the Faculty of Veterinary Medicine, Universiti Putra Malaysia. The vaccines manufactured by MVP are for the local and export markets in ASEAN, Asia and West African countries. Recently, MVP Life Sciences Sdn Bhd, the second vaccine company in Malaysia, was established to focus on the manufacturing of tissue culture based-vaccines and a new generation of vaccines using bioreactors and latest technology in vaccine production. Innovation to produce safe and effective poultry vaccines, which are also cheap, efficient and better, is the priority in local vaccine production. This can be achieved through advanced knowledge in animal biotechnology and molecular biology. It appears that conventional type vaccines will still be the main type of vaccine produced in the near future, but new generation vaccines hold the promise of more advantages although there is a big horizon to explore before this becomes a reality.

INTRODUCTION

The livestock industry in Malaysia has grown significantly from the year 2000 to 2009, at about 5.4% annually, with poultry and swine production dominating the local livestock scene with over 100% self sufficiency and contributing 94.73% of the total meat and eggs produced in the country (Idris and Rahim, 2010) (Figure, 1). It is indeed in line with the Third National Agricultural Policy (NAP3) launched in 1998, to increase the competitiveness of the agricultural sector in global trade and food security to ensure that there is sufficient and reasonably priced supply of basic food, and that each and every member of the family has access to enough food at any time to enable them to be active and healthy.

The poultry industry in Malaysia has evolved rapidly over the past 60 years almost on a similar pattern as that in advanced countries. The introduction of superior breeds, vaccines for disease control, high quality feed, advanced technology and favourable government policy have contributed to the transformation of subsistence poultry farming into a commercialized and advanced industry, with high productivity (Aini, 2005). The industry is run commercially by large-scale integrators and multi-national corporations. Peninsular Malaysia has been self sufficient in chicken meat production since 1960 and became a net exporter in 1983. The industry has grown at 5.95% annually with production increasing from 714,300 to 1.202 million metric tonnes from year 2000 to 2009, with total ex-farm value of RM5.468 billion or 53% of ex-farm value of the livestock industry. The total export of chicken products increased from RM54.44 million in 2007 to RM350.68 million in 2009. In addition, 510 million metric tonnes of eggs was produced in 2009 with total ex-farm value of RM2.226 billion or 22% of ex-farm value of the livestock industry (Idris and Rahim, 2010) (Figures, 1, 2). It demonstrated that the industry has played

its part in contributing to the realization of agriculture as the third engine of growth and creation of a high income economy which is the goal of the new economic model (NEM) and food security.

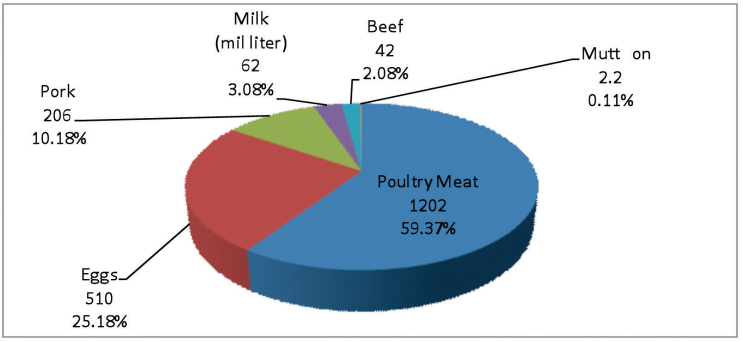


Figure 1 Production of livestock subsector in 2009 (X 10^3 MT). Source: Idris and Rahim (2010)

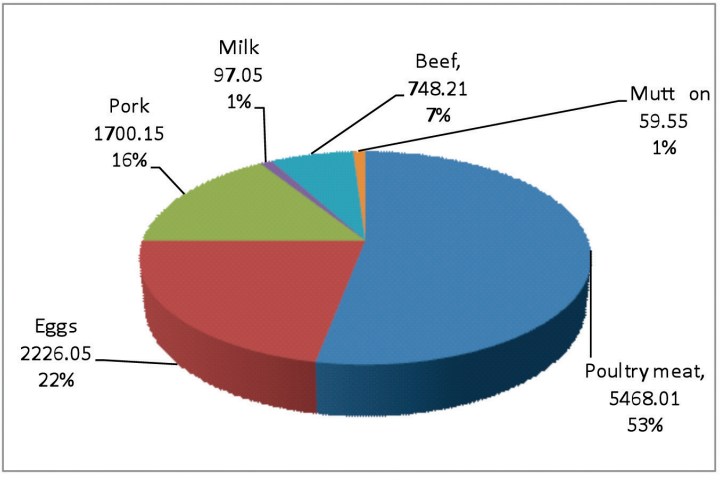
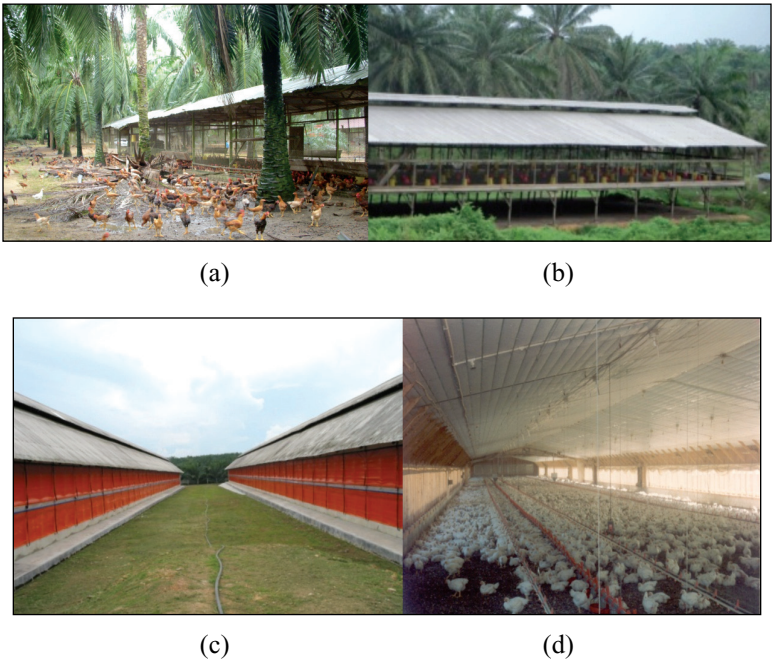


Figure 2 Ex-farm value of livestock subsector in 2009 (RM million). Source: Idris and Rahim (2010)

Chicken products have been a major source of protein which is relatively cheap, easily available and acceptable by most or majority of the society. The industry has not only provided enough healthy food to Malaysians, but also globally to people all over the world - we feed the world. The poultry industry is an example of a success story in the livestock industry in the country and could perhaps act as a model for the livestock industry in the country. However, the industry is not free from many issues and challenges such as high production costs and emerging and reemerging diseases. To date, the number of poultry farms, flock sizes and density have all increased remarkably due to increasing domestic consumption and export opportunities. The management and housing systems have also changed towards more intensive systems and large units (Figures, 3a, b, c, d). This development could invite high risk of disease outbreaks and limited production. The recent increases in the costs of production and outbreaks of highly pathogenic avian influenza (HPAI) further threaten the industry (Hair-Bejo *et al.,* 2006b). The worldwide movement of poultry breeding stock, poultry products, biologics, pet birds, free-flying migratory birds and waterfowls, are the additional means of introduction of disease agents from one country to another (Aini, 2005). As the commercial poultry industry continues to grow and change dramatically, to date almost all known major poultry diseases such as Newcastle disease (ND), infectious bursal disease (IBD), chicken anaemia virus (CAV), infectious bronchitis (IB), Marek's disease (MD), lymphoid leukosis (LL), fowl pox (FP), adenovirus infections (FAdV), reovirus infections, avian encephalomyelitis (AE), infectious laryngotracheitis (ILT), HPAI, salmonellosis, fowl cholera, mycoplasmosis, complicated chronic respiratory disease (CCRD) and coccidiosis, have been reported in Malaysia (Hair-Bejo, 1992, 2005a, b; 2006a, c; Chowdhury *et al*., 2002a,

b, 2003; Hasmah *et al*., 2003, 2004; Zamri-Saad and Hair-Bejo, 2006; Hair-Bejo et al., 2004b, 2005c; Hailemariam, *et al*., 2008; Ahmad *et al*., 2008; Jason *et al.,* 2008; Abubakar *et al.,* 2009; Tan *et al*., 2009a, b; Hair-Bejo and Bashir, 2010). Thus, without proper management programmes and appropriate intervention the health and production of chickens, as well as the quality and safety of the products, can be badly affected.



(a) (b)

(c) (d)

Figure 3 Poultry housing and management system. (a) Free rearing, (b) Open house and (c and d) Close house systems.

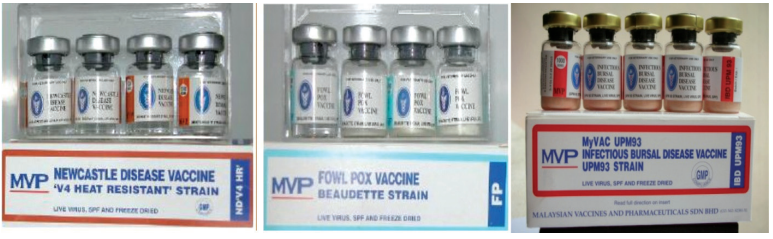
The economic impact of disease on the poultry industry comes not only from direct losses through death and interference with productivity but also from the cost of medication, vaccines, manpower and, in the case of some diseases, a ban on the export

of the meats, eggs and other chicken products. Successful chicken production depends to a significant degree on the health and prevention of diseases among the flock. Most disease problems in the chicken industry today are caused by interaction of many factors where immunosuppression plays a key role and is a frequent problem in chicken production (Jackwood, 1991).

Control and prevention of poultry diseases involves complex understanding of interaction of the agent, host and environment, and this usually can be achieved by proper biosecurity, vaccination and flock health programmes. Biosecurity encompasses management practices needed to prevent the spread of pathogens between farms and between buildings within a farm, and it is difficult and expensive to maintain a high level of biosecurity at all times. Thus, mechanisms involved in the defense against infections, especially viral infection has been shown to involve pathways of immunological reactions or vaccination. Ideally vaccines should induce lifelong protection against a pathogen without producing any signs of disease, reduce morbidity and subclinical infections, be safe, apathogenic, stable and easily delivered to a large number of chickens (Aini, 2005).

Three types of vaccines are available to the commercial poultry industry in Malaysia, namely the live attenuated and killed vaccines and the new generation of vaccines. Currently, Malaysia imports vaccines and pharmaceuticals worth RM 650 million annually and thus the Department of Veterinary Service is looking into ways of producing at least 30% of the total imported vaccines locally. There are 35 veterinary vaccine importers in Malaysia while Malaysian Vaccines and Pharmaceuticals Sdn Bhd (MVP) is currently the sole veterinary vaccines manufacturer in Malaysia. MVP manufactures 10 poultry vaccines against 4 important poultry diseases, namely, the NDV4, FP, IBD UPM93, IBD, NDF, NDS, NDB1, NDLasota, NDB1/H120 and NDLa/H120. Of these, 3 of the vaccines against 3

important poultry diseases, namely the NDV4, FP and IBD UPM93, are innovations from our research team at the Faculty of Veterinary Medicine, Universiti Putra Malaysia (Hair-Bejo, 2006b; Hair-Bejo *et al.,* 2006a) (Figures, 4a, b, c). The vaccines manufactured by MVP are used in local and export markets in ASEAN, Asia and West African countries, such as Indonesia, Thailand, Philippines, Hong Kong, Vietnam, Cambodia, Myanmar, Japan, Pakistan, Bangladesh, India, Egypt, Syria, Saudi Arabia, Kuwait, U.A.E, Timor Leste, Angola, Mozambique, Senegal, Ghana, Zambia, Sudan, Nigeria, Togo and Tanzania.



(a) (b) (c)

Figure 4 Three poultry vaccines which are innovation of UPM: (a) NDV4, (b) FP and (c) IBD UPM93.

We are also actively involved in research and development of new generation of vaccines against IBD, ND, CAV, IB and HPAI (Phong *et al*, 2007; Nurulfiza *et al*., 2006b; Lim *et al*., 2008; Jalilian *et al*., 2010). Research and development of new vaccines is vital to keep pace with the changes in the characteristics and pathogenicity of prevalent field viruses. Recently, a new spin-off or second vaccine company in Malaysia, namely, MVP Life Sciences Sdn Bhd, was established to focus on the manufacture of tissue culture based-vaccines and a new generation of vaccines using bioreactors and latest technology in vaccine production.

Knowledge of the pathogenesis of a disease is vital in understanding the pathogenicity and virulence of the agent, diagnosis of disease and development of safe and effective vaccines, in control and prevention of the disease. Our current and future innovations in poultry vaccines could ensure a safe and secure poultry industry in Malaysia and worldwide: Malaysian products for worldwide poultry disease control and prevention.

DISEASE

Disease is an adverse interaction between the agent, host and environment leading to structural or cellular damage (lesions) and functional abnormalities (clinical signs) (Figure, 5). The agent's ability to infect a specific host is genetically determined and many viruses infect only one particular species. For instance, infectious IBD virus (IBDV), IB virus (IBV) and ILT virus (ILTV) exclusively affect poultry. Others are less specific, such as the ND virus (NDV) which seems capable of infecting humans with mild lesions, whilst the HPAI virus (HPAIV) and influenza A virus (H1N1) can cause death in humans (Calnek *et al.,* 1991; Carlton and McGavin, 1995; Hair Bejo, 1995; Tan *et al*., 2009b; Abubakar *et al*., 2009).

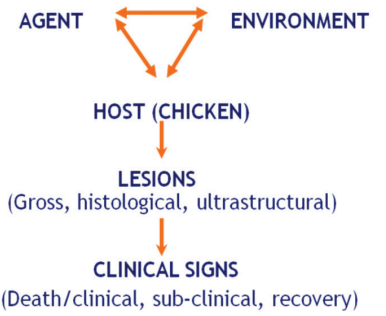


Figure 5 Concept and principle of disease.

Pathogenicity and virulence of viruses are determined by the virus genome. The virulence often depends on numerous factors such as adherence and antiphagocytic activity, and it is not surprising that it often depends on more than one gene. Changes in pathogenicity or virulence can take place easily, often involving only trivial changes in the genome. The presence of virulent markers in VP2 genes of IBDV, both in the restriction enzyme sites (*Bsp*M I, *Sty* I, *Taq* I, *Ssp* I *Sac* I and *Bst*N I) and amino acid markers (Ala [222], Ile [242], Gln [253], Ile [256], Ala [284], Ile [294] and Ser [299], and serine-reach hepapeptide ("SWSASGS"), differentiate very virulent (vv) IBDV from the classical and variant strains. These changes result in serious outbreaks of the disease, first reported in late 1980s despite vaccination using classical IBDV strains. Up till today IBD outbreaks due to vvIBDV is still commonly reported in both vaccinated and non vaccinated chicken worldwide (Hair-Bejo, 1992, 1993a, b,, 1994, 1996c; Carlton and McGavin, 1995; Chong *et al*., 2001; Hoque *et al.,* 2001a, b, 2002; Kong *et al.,* 2004a, b ; Phong *et al.,* 2002a, 2003; Sharma *et al.,* 2005; Tan *et al.,* 2004a,b, c; Bahmaninejad *et al.*, 2008; Nurulfiza *et al*., 2006a).

The pathogenicity of a virus is often dramatically altered following repeated growth of the virus under unfamiliar circumstances outside the body. The laboratory passage of pathogenic IBDV in cultured cells leads to great reduction in pathogenicity in chickens and this has been a standard procedure for the production of live attenuated virus vaccine (Khor *et al.,* 2004, 2005). Great reduction in the incidence of virus diseases in chicken is achieved through proper vaccination programmes in the farm. However, environmental factors such as biosecurity and stress factors also play a major role in the mechanism of virus infections (Liew *et al.,* 2003; Mims, 1990). Knowledge of the relationship of the lesions occurring in the

organs along with the cause and clinical signs, is vital in diagnosis of diseases (Hair-Bejo, 2005a).

DIAGNOSIS OF DISEASE

Diagnosis of poultry diseases can be achieved based on the history, clinical signs, gross and microscopic lesions and detection and/or isolation and characterisation of the agent. In addition, therapeutic diagnosis can be used in cases such as in nutritional deficiency or toxicity (Hair-Bejo, 1995). Viruses, bacteria, parasites, fungus and mycoplasma are some of the common infectious agents in poultry diseases, whilst for non infectious agents, chicken are at high risk from toxic materials, traumatic injury and deficiency of certain essential trace elements. The dose, route, species, strains, virulence and source of the agent could determine the occurrence and severity of the disease. Environmental factors such as the temperature, humidity, ventilation, stress, nutrients, housing, light and climate also play an important role in disease development (Liew *et al*., 2003). The age, sex, species, breed, immunity, disease and nutritional status of the chickens are a few important host factors in the development of disease.

The gross and microscopic lesions of diseases can be pathognomonic, typical, important or non-specific lesions, whilst the affected chickens may die or be presented with typical or non-specific clinical signs or sub-clinical signs such as increased (high) mortality or morbidity, poor feed conversion, retarded growth, reduced egg production, changes in egg quality, low fertility and poor hatchability (Hair-Bejo, 1994, 1995, 2002; Hair-Bejo *et al*., 2005b). Diseases, whether clinical or sub-clinical are therefore an obvious deterrent to productivity. Thus, disease monitoring programmes, investigation and control are important to reduce the risk of losses, recommend measures for treatment and prevention,

and to control the factors causing disease and their interaction, respectively (Hair-Bejo *et al*., 2006b).

PATHOGENESIS OF DISEASE

The effect on the interaction between the agent, host and environment at any step on the mechanisms of disease development is the major factor in determining disease production. Knowledge of the pathogenesis of a disease is vital in understanding the pathogenicity and virulence of the agent, diagnosis of disease and appropriate intervention in control and prevention of the disease (Figure, 6).

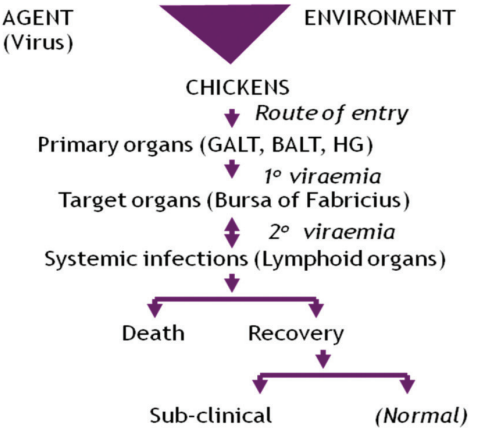


Figure 6 Concept and principle of pathogenesis of disease.

Route of Entry and Defence Mechanism of the Host

Respiratory, gastrointestinal and intra-ocular routes are the most common pathways for agent infection in poultry. A mucociliary epithelium covers most of the surface of the lower respiratory tract.

It consists of single ciliated cuboidal and columnar cells together with single mucous secreting cells and subepithelial mucous secreting glands. Any foreign particles deposited on this surface epithelium can be entrapped in the mucous and borne upwards from the lungs to the back of the trachea by ciliary action. The nasal cavity of the upper respiratory tract has a similar mucociliary epithelium and any particles deposited there can also be carried to the back of the oral cavity and be swallowed or sneezed out from the cavity. Aggregations of lymphoid cells are also present in the lamina propria of the respiratory tract. These lymphoid cells play an important role in defence mechanisms against infectious agents. In contrast, it could also facilitate the entry of the agents, such as a virus, into the body. NDV, IBV, ILTV and HPAI are some viruses that commonly use the respiratory tract as the route of entry to cause infection in the host (Hodges, 1974; Cotran *et al.,* 1989; Mims, 1990; Hair-Bejo, 2005a).

Contamination of feed and water, as well as various other swallowed materials originating from the mouth, nasopharynx and lungs, with infectious agents such as IBDV and CAV, would allow these pathogenic viruses to enter the body through the gastrointestinal route. The success of infection through the gastrointestinal tract is certainly affected by the presence of mucous, acid, enzymes and bile. Mucous protects epithelial cells, perhaps acting as a mechanical barrier to infection and contains secretory IgA antibodies that protect the immune chickens against infection. Viruses infecting by the intestinal route, such as IBDV, are often capable of surviving in the presence of acid, proteolytic enzymes and bile. IBDV is a nonenveloped single-shelled icosahedral capsid and is very resistant to physical and chemical agents (Hair-Bejo *et al.,* 2004a, d).

The morphology and epithelial lining of the intestinal tract is slightly different from the respiratory tract. The surface is made up of villi and crypt which is always in motion with constant changing of the epithelial cells or the enterocytes. Thus particles in the lumen are moved about a great deal. Infectious agents such as viruses are multiplied only in living cells and thus virus infection through the intestinal tract must make the most of what are primarily chance encounters with epithelial cells. The virus may form firm unions with receptor substances on the surface of intestinal epithelial cells, thus giving time for the penetration of the virus into the cells. Penetration of the virus into the cells may take place either by phagocytosis of the virus particle or by fusion of the virus surface with the cell membrane so that the contents of the virus particle enter the cells. Most epithelial cells, either respiratory or intestinal, are capable of pahgocytosis, but this is in small scale compared with specialist phagocytes, the macrophages and polymorphonuclear leucocytes. In chickens, lymphoid cell aggregations lay immediately below the intestinal epithelium at the lamina propria. The morphology of this lymphoid cell aggregation is almost similar to those of Payer's patches in mammals. The epithelial lining within the lymphoid cell aggregation is highly specialized, the so called M cells. These M cells can take up particles and foreign proteins, delivering them to underlying immune cells with which they are intimately associated by means of cytoplasmic processes. A similar role could be played by the inter-epithelial leuckocytes (Hodges, 1974; Riddell, 1987; Mims, 1990; Hair-Bejo *et al*., 2004c).

In the ocular region, the head-associated lymphoid tissues (HALT) or conjunctiva-associated lymphoid tissues (CALT) play an important role for initiation of virus infection. The HALT consists of two major lymphoid organs, namely the Harderian gland and CALT. The aggregations of these lymphoid tissues are important

for local immunity in the paraocular region of chickens as well as entry of agents into the body to cause infection. The ocular region and conjunctiva is kept moist and healthy by the continuous flow of secretion from the lachrymal and other organs. The secretions contain lysozyme, IgA and other antimicrobial substances and this may inhibit the opportunity for initiation of infection in the region. Infectious agents present in the ocular region may also be treated like inanimate particles of dirt or dust and be swept away via tear ducts into the nasal cavity (Hodges, 1974; Hair-Bejo *et al.,* 2005b).

Primary Virus Entry and Replication

Some of the most successful viruses such as ILTV and FP multiply in the epithelial surface of the respiratory tract and skin, respectively at the site of entry into the body, producing a spreading infection in the epithelium which is shed directly to the exterior. This is the simplest, most straightforward type of microbial parasitism. It takes at least a few days for antibodies or immune cells to be formed in appreciable amounts and delivered to the site of infection. The epithelial cells may be destroyed and inflammatory responses induced, but there is little or no virus invasion of underlying tissues. The infection is terminated partly by non immunogical resistance factors, and partly because most locally available cells have been infected. Interferons are important nonimmunological resistance factors. They are low molecular weight proteins, coded by the cell, and formed in response to infection with nearly all viruses. The interferon formed by the infected cell is released and can act on neighbouring or distant cells, protecting them from infection (Mims, 1990; Hair Bejo, 1995).

However, for viruses that cause systemic infections and where the main target organ is away from the first site of entry or infection, the virus must first enter the blood or lymph. This means that after

gaining access through the epithelial lining of the respiratory or gastrointestinal tract or others, the virus needs to enter into the lumen of subepithelial lymphatic or blood vessel, either as a free virus or, alternatively, bounded within mobile cells or leucocytes that will carry it to other parts of the body or the target organ. The virus cannot replicate until it reaches a susceptible or target cells and in the absence or shortage of such cells infection would fail or be seriously hindered in spreading through the body and thus there will be failure of disease development (Hair-Bejo *et al.,* 2004c, 2005b).

In virus infection, after entering the epithelial cell layer, the virus encounters the basement membrane. This membrane acts as a filter and to some extent can hold up the infection. However, following infection, functional integrity of the membrane is always damaged by inflammation or epithelial cell necrosis. Thus the invading virus is exposed to the host defence system, tissue fluids, lymphoid aggregation and phagocytic cells, as it reaches the subepithelial tissues. The interaction between the virus and the host defence system, especially the phagocytic cell, is a central feature of infection and pathogenicity. Phagocytes are designed to ingest, kill and digest invaders and the course of the infection depends on the success with which this is carried out. Virulent viruses have developed a great variety of devices for countering or avoiding the antimicrobial action of phagocytes. Viruses produce inflammatory products in tissues in the form of necrotic host cell materials or antigen-antibody complexes. Mononuclear infiltrates are also favoured in virus infections because the infected tissues themselves are often one of the sites for the immune response, with mononuclear infiltration and cell division (Cotran *et al.,* 1989; Mims, 1990; Carlton and McGavin, 1995).

Primary and Secondary Viraemia

The blood is the most effective vehicle of all for the spread of infectious agents such as viruses throughout the body. After entering the blood the virus can be transported within a minute or two to a vascular bed in any part of the body. In systemic virus infection the epithelial surface at the first site of entry is traversed and the virus reaches the blood at an early stage, either via lymphatics and lymphoid cells or after entering the subendothelial blood vessel. The virus is then spread through the body via the blood stream, usually without any signs or symptoms. The virus may be carried freely in the plasma, in the form of elements of blood or in both compartments. The amount of virus at any given time may be negligible. This is called primary viraemia and is a common silent event often only known to have taken place because of invasion at a distant target organ. The localization of the virus in the organ depends on the ability of the virus to adhere to or grow in vascular endothelial cells and on phagocytosis by reticuloendothelial cells. The virus must also be resistant to any antimicrobial factors present in the plasma (Carlton and McGavin, 1995; Cotran *et al.,* 1989; Mims, 1990).

After growth in the target organs there is a reseeding of the virus into the blood once again to give a secondary viraemia and infection of a fresh set of tissue. The secondary viraemia is of larger magnitude and often easily detected in blood samples. Viruses in circulation are exposed to phagocytosis by reticuloendothelial macrophages as long as they are free in the plasma. Killing of the virus could mean termination of the infection, whereas virus persistence and growth in macrophage could lead to infection in the organ harbouring the macrophages, with reseeding of progeny microorganism into the blood. The circulating virus could also invade the tissue by adhersion into the endothelial blood vessels,

preferably capillaries or venules, where circulation is slowest and the vessel wall thinnest. The virus then can reach tissues by leaking through the vessel wall, being passively ferried across the wall or by growing through the vessel wall. Protection of tissues from invasion by circulating viruses depends to some extent on the anatomical nature of the blood-tissue barrier or junction. One of the most important barriers to the spread of the virus into an organ is a layer of insusceptible cells that cannot be infected either through the capillary endothelial itself or other cells in extravascular tissues. Even if vascular endothelium is infected, subsequent events may be determined by the topography of budding. Viruses released exclusively from the luminal surface of the cell would contribute to a viraemia, but unless the cell is destroyed, tissue invasion would depend on liberation of the virus from the tissue side of the endothelial cells (Hair-Bejo *et al.*, 1997).

Capillaries in the central nervous system, connective tissue, skeletal and cardiac muscles are lined by a continuous layer of endothelium whereas those in renal glomerulus have fenestrated gaps in the endothelium. Once viruses have localized in the vessel wall, passage across the endothelium might be expected to be easier when there are fenestrated gaps. In all cases however, there is well defined basement membrane which must also be negotiated if viruses are to reach extravascular tissues. Circulating viruses localize readily on the capillary endothelium in inflamed areas or during repair of injury and on not well developed capillaries during foetal development. However, for localization in normal capillaries they must circulate in the blood long enough and in high enough concentrations. Therefore the faster the clearance of viruses from the body, by reticuloendothelial cells, the less chance there is for localization in capillaries. Removal of circulating viruses by reticuloendothelial cells, or their inactivation by serum antibody

and complement, constitutes the most important barrier to invasion of those organs that have the capillary bed. In a capillary which is well developed or not inflamed, initial localization of the virus presumably depends on attachment to receptors on endothelial cells (Cotran *et al.,* 1989; Mims, 1990; Carlton and McGavin, 1995).

Cell and Tissue Damage in the Target and Other Organs

The impact on the host due to viral infection depends very much on the tissue involved. The central nervous system is particularly vulnerable to slight damage. However the effect on tissue is much less in the case of organs such as the liver or kidney, which have considerable functional reserves. More than two thirds of the liver must be removed before there are signs of liver dysfunction. Cell damage has profound effects if it is the endothelial cells of small blood vessels which are involved. The resulting circulatory changes lead to anoxia or ischemic necrosis in the tissues supplied by the vessels. Cell and tissue damage is sometimes due to the direct local action of the virus. When the virus grows in cells it causes early shutdown of RNA, protein and DNA synthesis in the host cell. Within a few hours there is an inevitable cytopathic effect and the cell dies (eg. pox viruses and herpes virus). Viral proteins accumulating in the cells during replication possibly have a toxic effect and contribute to cell damage. Cell membranes are generally the site of the initial damage, and interference with membrane function causes a leakage of cell material through the cell surface to the exterior and when lysosomes are affected there is lysosome enzyme leakage into cytoplasm and the cell undergoes autolytic destruction (Carlton and McGavin, 1995; Cotran *et al.,* 1989; Mims, 1990).

The lesions in cells infected with viruses are generally non specific. The most common and potentially reversible change

is hydropic degeneration due to changes, particularly in the mitochondria. In irreversible conditions apoptosis and necrosis may occur. The nuclear chromatin moves to the edge of the nucleus (margination of chromatin) and becomes condensed (pyknosis). The presence of intranuclear and/or intracytoplasmic inclusion bodies under histological examination of the infected tissues is a quiet characteristic of virus infection. The inclusion often represents either cell organelles or virus factory in which viral components are being synthesized and assembled. Herpes virus (ILTV) and adenovirus (inclusion body hepatitis (IBH)) infections in chickens form intranuclear inclusions and pox viruses form intracytoplasmic inclusions (Figures, 7a, b). In ILTV infection syncytia intranuclear inclusion bodies are formed. Under ultrastructural examination, intracytoplasmic virus inclusions are commonly seen during active infection and replication of many viruses such as in IBDV infection (Hair-Bejo, 1995, 2005b; Voon *et al.,* 2004).

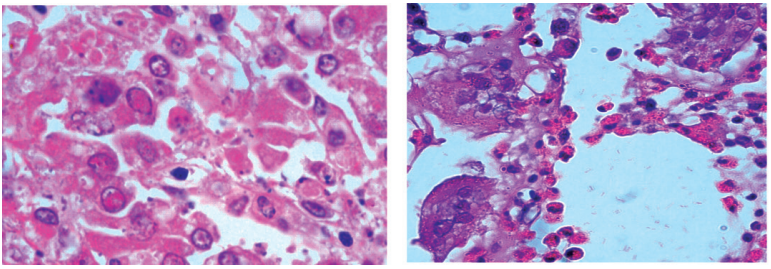


Figure 7 Intranuclear inclusion bodies. (a) IBH and (b) ILT. HE, 1000X.

The combination of antibody with antigen is an important event, initiating inflammatory phenomena that are inevitably involved in the expression of the immune response. In the infected host, those inflammatory phenomena are most of the time of great antimicrobial value, but they are nevertheless immunopathological features of

the infection, and immune complex reactions sometimes do a great deal of damage in the infected individual. The sequela of the reaction depends to a large extent on the size and the relative proportions of antigen and antibody. If there is a large excess of antibody, each antigen molecule is covered with antibody and is removed rapidly by reticuloendothelial cells which have receptors for the antibody molecule. When equal amounts of antigen and antibody combine, lattice structures are formed and these form large aggregates whose size ensures that they are also rapidly removed by reticuloendothelial cells. If, however, such as in corona virus infection (IB), complexes are formed in antigen excess, the poorly coated antigen molecules are not removed by reticuloendothelial cells. The molecules continue to circulate in the blood and have the opportunity to localize in small blood vessels elsewhere in the body such as the glomuruli. In the glomeruli the complexes pass through the endothelial pores and are deposited beneath the basement membrane. The localization of immune complexes and complement in the glomeruli can be associated with a local inflammatory response. There is an infiltration of polymorphs, swelling of the glomerular basement membrane, which may lead to membranous glomerulonephritis and glomerulosclorosis as well as severe necrosis of the renal tubules and deposition of urates in the affected area resulting to severe nephritis (Mims, 1990; Hair-Bejo, 1995).

Certain viruses such as the herpes virus (Marek's disease) and retroviruses (Lymphoid leukosis, Avian leukosis sub-group J (ALV-J)) undoubtedly cause tumors and this is to be regarded as a late pathological consequence of infection. The tumor virus genome can be integrated into the host cell genome, whether a tumor is produced or not, so that the virus becomes a part of the genetic constitution of the host. Sometimes the host cell is transformed

by the virus and converted into a tumor cell, the virus either introduces a transforming gene into the cell or activates expression of a pre-existing cellular gene. The transforming genes of DNA viruses generally code for T antigens which are necessary for transformation, and the transforming gene of RNA tumor viruses are known as *onc* genes (oncogenes) (Mims, 1990; Hair Bejo, 1995; Hair-Bejo *et al.,* 2004b; Thapa *et al.,* 2004a, b).

Death or Recovery from Virus Infection

If there is to be recovery from infection, it is first necessary that the multiplication of the infectious agent be brought under control. The viruses must decrease in numbers and cease to spread through the body or cause progressive damage. This is accompanied by other factors, especially immunological factors. Otherwise the chicken will die due to failure of the vital organ/s resulting from the development of severe lesions in the organs due to the infection. In the process of recovery from an infectious disease, damaged tissue must be repaired and reconstituted. Sometimes the virus is completely destroyed and tissue sterilized, but often this fails to take place and the virus persists in the body, in some instances continuing to cause minor pathological changes and may cause persistent infections (Hair-Bejo, 1994, 1995; Hair-Bejo *et al.,* 2004c)

The antibody plays a major part in the process of recovery in virus infections, especially for those viruses producing systemic diseases. The circulating specific antibodies will coat the surface of the free virus particles attachment to receptors of the target cells and thus it prevents infection from taking place. Antibodies that combine with the virus surface often block attachment and thus prevent infection of cells. Some attachment is not blocked, but the antibody nevertheless interferes with virus entry into the cell or with subsequent replication of the virus. The antibody also

promotes the uptake and digestion of virus by phagocyte cells, so that the virus-antibody complex is finally taken up and disposed off. Antibodies neutralizing virus infectivity are called neutralizing antibodies. Antibodies also act against viruses by clumping them, by destroying them with complement or by inducing inflammatory responses following their interaction with viral antigen (Cotran *et al.,* 1989; Mims, 1990; Carlton and McGavin, 1995).

The cell mediated immunity (CMI) also plays an important role in the process of certain virus infections, such as in the herpes and pox virus infections. Antibodies can neutralize free virus particles liberated from cells, but often fail to influence events in infected cells. Action on the infected cell seems necessary for recovery in some virus infections. The destruction of cells infected with viruses take place in various ways, but mainly depends on the mechanism of virus maturation in the cell. Many viruses such as IBDV replicate and produce fully infectious particles inside the cytoplasm. These particles are nucleocapsids, consisting of the basic nucleic acid core with its protein coat (capsid), and they are liberated from the cell and exposed to antibodies when it dies and disintegrates. Other viruses such as herpes viruses and paramyxo viruses do not have to wait for cell disruption, but are liberated by a process of budding through the cell membrane. The basic viral nucleocapsid in the cytoplasm becomes closely associated with the cell membrane, causing viral antigen to be incorporated into it. The virus particle finally matures by budding through the altered cell membrane, acquiring an envelope as it does so (Hair-Bejo, 1993; Mims, 1990). In herpes type virus infections, virus antigen appear on the surface of the infected cells 12 - 24 hours before virus multiplication is completed, so that the cells can be destroyed early by CMI. Herpes viruses tend to spread directly from the cell without entering extracellular fluids, and antibodies cannot enter cells to

neutralize the virus. By acting directly on infected cells, immune cytolysis helps prevent this type of spread. Immune cytolysis has a similar action on cells infected with pox viruses. It appears that at the site of virus multiplication, T lymphocytes, in the course of their normal movement through the body, encounter virus antigens that have become bound to the surface of a macrophage or other antigen-presenting cell. When a T cell encounters the antigen to which it is specifically sensitized, the CMI response is initiated. The T cell differentiates and divides to give fresh supplies of specifically T cells. Lymphokines are liberated to attract macrophages and other leukocytes and focus them onto the site of infection. The infected cells are destroyed by cytotoxic T lymphocytes and other cells, and the virus material and cell debris is phagocytosed and disposed by activated macrophages. Once the multiplication of the infecting virus has been controlled, and the virus itself perhaps eliminated from the body, the next step in the process of recovery is to tidy up the debris and repair the damaged tissues (Cotran *et al.,* 1989; Mims, 1990; Carlton and McGavin, 1995).

INFECTIOUS BURSAL DISEASE

Infectious bursal disease (IBD) or Gumboro disease is an important highly contagious immunosuppressive viral disease of chickens which poses a significant economical threat to the industry due to high mortality and immunosuppression (Hair-Bejo *et al*., 2004c). The disease was first recognised as a clinical entity in 1957 in USA (Cosgrove, 1962). Since then, IBD outbreaks have been reported worldwide, but have been relatively under control due to proper immunization programmes in poultry farms. However, in the 1980s very virulent (vv) and variant (va) strains of IBD virus (IBDV) emerged, which have caused serious disease problems in many countries over the past decade (Van Den Berg, 2000; Hair-

Bejo, 1993a; Chettle *et al*., 1989; Stuart, 1989). Many reported that vvIBDV are antigenically similar to the classical strains (caIBDV) (Synder 1990), but it is able to establish infection at high levels of maternal antibody which is usually protective against caIBDV strains (Chettle *et al*., 1989). Chickens which received IBD vaccine of caIBDV origin could not be protected against vaIBDV infections. The characterization of IBDV field isolates during disease outbreaks is vital for the right use of IBD vaccine and effective control and prevention of the disease. The caIBDV and vvIBDV strains cause moderate (25%) and high (75%) mortality, respectively, as well as immunosuppression in susceptible chickens, whilst the vaIBDV strains mainly cause immunosuppresion with relatively low mortality (5%) (Hair-Bejo, 1994).

IBDV is a double stranded ribonucleic acid (dsRNA) virus in the genus of *Avibirnavirus* within the family *Birnaviridae* (Pringle, 1999; Dobos *et al*., 1979). The target organ of the virus is the bursa of Fabricius, an important organ in the young chickens' developing immune system. IBDV replicate and destroy the immature B-lymphocytes of the bursa of Fabricius resulting in severe and prolonged immunosuppresion. IBDV is a small, single capsid shelled non-enveloped virion with icosahedral symmetry, approximately 60nm in diameter (Hirai and Shimakura, 1974). The virus is very stable and relatively resistant physical and chemical agents (Mc Ilroy *et al.,* 1989). The genome of the virus is designated as A and B (Hudson, 1986; Azad *et al*., 1985). Segment A (~3.4 kb) contains two open reading frames (ORFs) of 3,039bp and 438bp, which partially overlap at the 5' end of the genome (Azad *et al*., 1985). The large ORF encodes a precursor polyprotein (NH_2-VPX-VP4-VP3-COOH), which is autoproteolytically processed by cis-acting viral protease VP4 into VPX, VP3, and VP4 (Mundt *et al*., 1995). The VPX, VP2 and VP3 form the virus capsid. Highly

conformational epitopes were present in the VP2 protein that are responsible for induction of host neutralizing antibodies to confer protective immunity (Fahey *et al.,* 1989). The VP2 gene is therefore an important target for cloning and expression which have high potential to be used for the development of subunit vaccines. VP3 is the minor structural protein recognized by the non-neutralizing antibodies (Becht *et al.*, 1988). Smaller ORF in segment A encodes the VP5 protein (Bayliss *et al.,* 1990). The VP5 may be important in the pathogenesis of IBD since experimentally induced VP5-defective virus was unable to cause bursal lesions. Segment B (~2.8 kb) has single ORF encodes for the viral RNA-dependent RNA polymerase (RdRp) (Muller *et al.,* 1979).

Pathogenesis and Pathogenicity of IBDV

Pathogenesis of disease is the sequence of events of an infectious agent starting from the point of entry to the host, to the entire development of lesions and appearance of the clinical signs. Knowledge on the pathogenesis of disease is vital in understanding the pathogenicity and virulenct of the agent, and in the diagnosis, treatment, control and prevention of the disease, to ensure good performance and health of the chicken, and minimal losses of production due to disease outbreaks (Hair-Bejo, 2005a). The gastrointestinal tract and intra-ocular routes are the most common pathways for IBDV infection in chickens. Contamination of feed and water, as well as various other swallowed materials originating from the mouth, nasopharynx and lungs, with IBDV would allow this pathogenic virus to enter the body through the gastrointestinal route. The success of infection through the gastrointestinal tract is certainly affected by the presence of mucous, acid, enzymes and bile. However, IBDV is often capable of surviving in these conditions. The virus will later attach and primarily replicate in the

lymphoid cell aggregations of the gut associated lymphoid tissues (GALT) (Hair-Bejo *et al*., 1997, 2000b, c, 2004d) (Figures, 8a, b). In the ocular region, the head-associated lymphoid tissues (HALT) or conjunctiva-associated lymphoid tissues (CALT) play an important role for initiation of virus infection. The HALT consists of two major lymphoid organs namely the Harderian gland and CALT (Figures, 8c, d). The aggregations of these lymphoid tissues are important for local immunity in the paraocular region of chickens as well as entry of viruses into the body to cause infection (Thu-Zar *et al*., 2000; Hair-Bejo *et al*., 2005a).

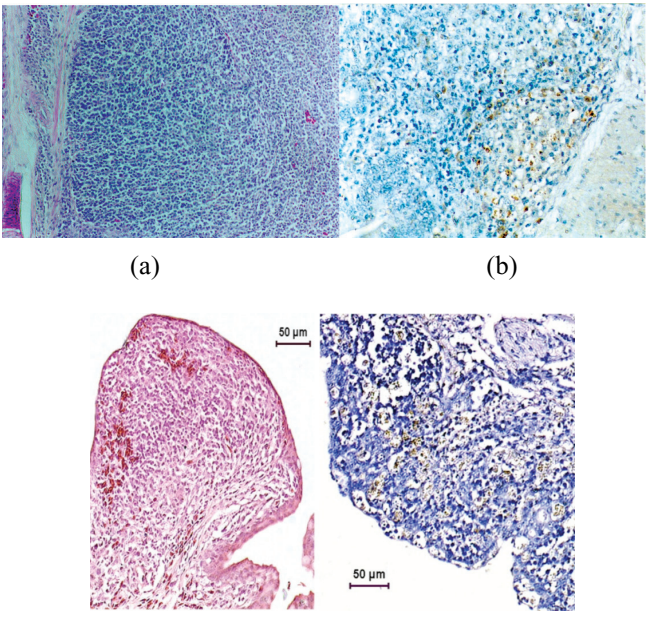


Figure 8 Primary replication of IBDV at site of entry. GALT (a) Control. HE, 200X, (b) IBDV infected GALT: positive for IBDV. Immunoperoxidase staining (IPS), 200X. CALT (c) Control. HE, Bar = 50*u*m, and (d) IBDV infected CALT: positive for IBDV. IPS, Bar = 50*u*m.

Following primary replication of the virus in the lymphoid tissues, at the first site of entry or infection, the virus will enter the blood circulation to get access into the target organ. This is called primary viraemia and is a common silent event, often only known to have taken place because of invasion at a distant target organ, the bursa of Fabricius. After massive replication of the virus in the target organ, there is a reseeding of the virus into the blood to give a secondary viraemia and infection of a fresh set of tissue (Hair-Bejo *et al.,* 1997; Hair-Bejo *et al.,* 2005a; Roosevien *et al.,* 2005; Tasfaheywet *et al*., 2008) (Figures, 9a, b, c).

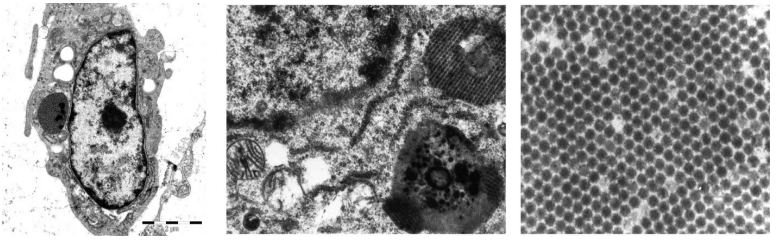


Figure 9 Replication of IBDV in the lymphoid cells of the bursa Fabricius. (a) Intracytoplasmic inclusion body. TEM, Bar = 2*u*m. (b) Virus particles emerged from the inclusion bodies. TEM, 60K. (c) IBDV particles. TEM, 80K.

The impact on the chicken due to different strains of IBDV infection depends very much on the tissue involved. Severe damagd of the lymphoid organs/tissues during secondary viraemia and thereafter, due to vvIBDV infection, could lead to high mortality and severe immunosuppression in the surviving chickens (Figures, 10a, b, c, d). In contrast, the lesions caused by caIBDV infection is rather less severe when compared to the vvIBDV infection and immunosuppresion recorded if the chicks were infected with the virus at below 2 to 3-weeks-old, while if the infection occurs at a later age, it could cause lowes percentage of mortality than the

vvIBDV infections. The vaIBDV only causes immunosuppresion and damagd of the lymphoid organs, especially the bursa of Fabricius. The infected chicken is highly susceptible to other pathogenic pathogens and died later due to secondary infection (Hair-Bejo, 1994).

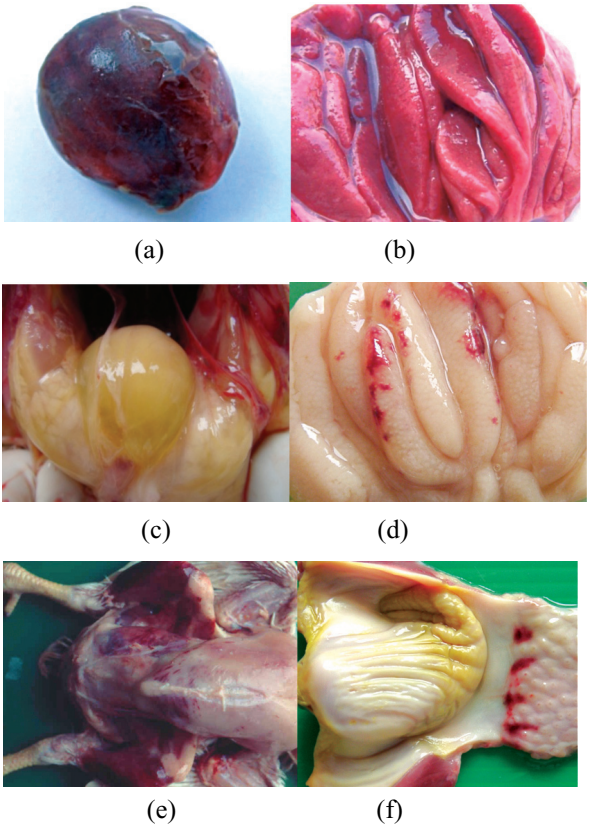


Figure 10 Typical gross lesions of chicken infected with vvIBDV. (a and b) Haemorrhages of the bursa Fabricius, (c and d) Gelatinous materials covering the serosal surface of the bursa Fabricius, and necrosis and haemorrhages of the mucosa, (e) Haemorrhages of muscles, and (f) Haemorrhages of the mucosa at the junction between proventriculus and gizzard.

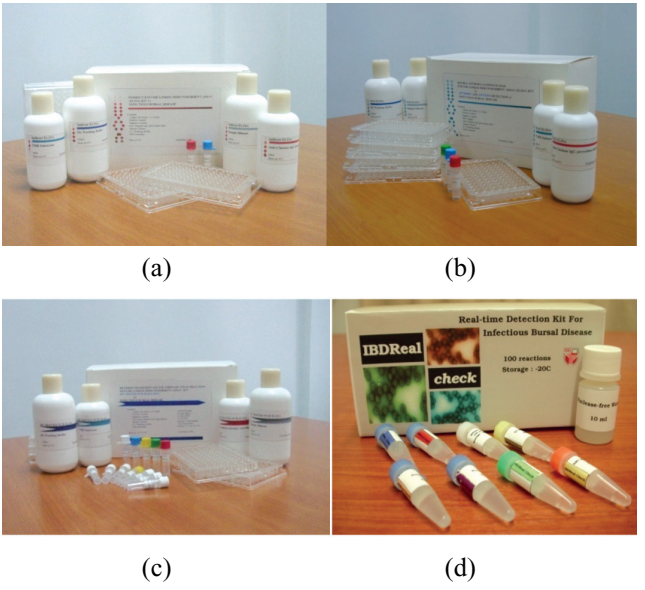
It is interesting to note that the interaction between the agent, host and environment at any steps during the mechanisms of disease development is the main factor to determine disease production. Any intervention at any of the steps could prevent the occurrence of disease and is the principle for disease control and prevention.

Detection and Characterisation of IBDV

Microscopic examination of the bursa of Fabricius with lesion scoring is useful and can be routinely used in diagnosis of IBD especially when other diagnostic aids are not available (Hair-Bejo, 1993; Hair-Bejo *et al.* 2005b), although in principls other specific tests are required to confirm the diagnosis. It is fast, cheap and can be easily made available and can also be used in the monitoring of vaccination efficacy (Hair-Bejo, 2002; Hair-Bejo *et al.*, 2005b). It is important to note that the severity of lesions in the bursa of Fabricius is an important indicator to determine the immunosuppressive effect of the virus. Bursa of Fabricius is a central lymphoid organ of chickens and the target organ for all strains of IBDV. It was reported that a few live IBD vaccines could induce high levels of IBD antibody, but at the same time cause severe bursal lesions. Thus, the chickens will be protected against IBDV field challenged, but is also immunosuppressed and highly susceptible or dies due to secondary infection by other pathogens (Hair-Bejo, 1994). Thus, examination of bursal lesions is a must to ensure the efficacy of IBD vaccines. The usage of immunohistochemistry and electron microscopy techniques in the detection of the agent or antibody against IBDV could confirm diagnosis of IBD outbreaks (Hair-Bejo *et al*., 2004c), although the technique is not always available.

Recently, various types of enzyme-linked immunosorbent assay (ELISA) techniques namely, indirect, double antibody sandwich (DAS) and reverse transciptase nested polymerase chain reaction (RT-Nested PCR) ELISAs, to be used in the diagnosis

and monitoring of IBD, were successfully developed (Phong *et al.,* 2002b, 2003; Hair-Bejo *et al*., 2006d, e, f; Nurulfiza *et al.*, 2008). The development of polymerase chains reaction (PCR) methods, namely reverse transciptase PCR (RT-PCR) and restriction fragment length polymorphism (RFLP) assay, and the use of various bioinformatics software enabled us to detect and holistically characterise IBDV strains (Chong *et al*., 2001; Hoque *et al*., 2001, 2002; Phong *et al.,* 2002b; Tan *et al*., 2004a; Khong *et al*., 2004a, b; Sharma *et al*., 2004, 2005; Hair-Bejo *et al*., 2006g; Nurulfiza *et al.*, 2006a;, b, c; Bahmaninejad *et al.,* 2008), and determine the source of origin. A more rapid and sensitive SYBR Green I based real-time PCR was also developed for rapid detection, quantification and differentiation of IBDV subtypes (Omar, 2005; Hair-Bejo *et al.,* 2006c, Hairul-Aini *et al*., 2008) (Figures, 10a, b, c, d).



(a) (b)

(c) (d)

Figure 11 Diagnostic kits for IBD invention of UPM. (a) Indirect ELISA, (b) DAS ELISA, (c) RT-Nested PCR and (d) SYBR Green I based real-time PCR.

IBD Vaccines and Vaccination

Three types of vaccines are currently available to the commercial chicken industry: the live attenuated and killed vaccines, and the new generation of recombinant vaccines. The aims of vaccination are for the B cells to synthesise and secrete antibodies that could neutralise invading agents or serve as anchor molecules for cellular cytotoxicity. T cells are necessary for optimal B cell response. Though B cells are able to respond to free antigen, an optimal response will only be achieved if at the same time an efficient T helper response is induced. Therefore, every successful vaccination should also aim at T cell activation. The ultimate goal of vaccination is to induce an immune response that will protect chickens directly by the induction of antibody and cell mediated immunity, and result in the induction of immunological memory. A subsequent infection by virulent organisms either fails to cause disease in the face of active immunity or induces a rapid memory response that clears the infection without loss of performance. Vaccination should be carried out at a time when the host is immunologically competent. A rational vaccination programme also requires the vaccine antigens to be presented in the most immunogenic form (Omar, 2005). Ideally, vaccines should induce lifelong protection against a pathogen without producing any signs of disease, and reduce morbidity and subclinical infections. Vaccines must also be safe, apathogenic, stable and easily delivered to large numbers of chickens (Hair-Bejo *et al*., 2004b, e, 2006a; Hair-Bejo and Aini, 2008).

Vaccination is the major tool for the prevention and control of IBD in the poultry industry. Types of vaccine, time of vaccination, level of maternally derived antibody in the chicks and IBDV field strains are some important factors to be considered to ensure effective vaccination programmes (Hair-Bejo *et al.,* 2004b, e; Chulan *et al.,* 1998; Zulkifli, *et al*., 1997). Some chickens immunized with live

attenuated IBD vaccines showed a certain degree of bursal atrophy and immunosuppression that interferd with other vaccinations (Hair-Bejo *et al*., 2006a; Tsukamoto *et al*., 1995; Muskett *et al*., 1985). Live attenuated vaccines are usually developed from the field or wild virus attenuated in chicken embryonated eggs or tissue culture. The vaccine virus could replicate effectively in the target organ of the chickens and could induce protective immune response similar to natural infection. However, it may have the risk associated with the potential for reversion to a virulent phenotype (Muskett *et al*., 1985). Inactivated or killed vaccines are typically safe, but less effective than live attenuated vaccines (Van den Berg, 2000). The vaccine virus is not able to replicate in the chickens and the immune responses of the virus can be enhanced by adjuvants and immunomodulators such as the conventional oil based adjuvants, plant extracts, bacterial products, toxins, various cytokines and genes with immunomodulator effects such as TLR, HSP and CpG (Omar, 2005).

Alternatively, in recent years, the recombinant technology to express structural proteins of IBDV has been used as subunit vaccines. A subunit vaccine overcomes the risk of reversion. As the main host protective antigen harboring most of the neutralization sites, VP2 has been used for the development of subunit vaccines and has been expressed in a number of systems such as avian herpesvirus vector (Tsukamoto *et al*, 2002), fowlpox virus vector (Shaw and Davison, 2000), fowl adenovirus vector (Francois *et al.,* 2001), Marek's disease virus vector (Tsukamoto *et al.*, 1999) and Semliki Forest virus vector (Phenix *et al.*, 2001). However, these methods are costly and complicated. Alternatively, expression of VP2 as the recombinant protein in systems including *E. coli* (Rong *et al*., 2005; Rogel *et al*., 2003), yeast (Pitcovski *et al.,* 2003) and insect cells (Dybing and Jackwood, 1998) were explored. VP2

expressed in yeast and insect cells proved to be effective, but the cost is high. Alternatively there is production of virus-like particles of IBDV, where the virus-like particles resemble the native viral capsids structurally and immunologically and elicit excellent antibody responses (Kibenge *et al.,* 1999), but the cost of production and risk of reversion are also high. In contrast, the *E. coli* expression system is still known to be the fastest, easiest and an inexpensive technique used to express usable amounts of recombinant protein, although it has been reported that the recombinant VP2 expressed in *E. coli* is often hampered by low expression levels and low solubility. In contrast, improved expression level and solubility has been reported in other studies and a recombinant VP2 gene of vvIBDV cloned into an *E. coli* expression system vaccinated in specific pathogen free (SPF) chickens could provide 75-100% protection against vvIBDV challenged (Nurulfiza *et al.,* 2006b; Omar *et al*., 2006; Saadun *et al.,* 2005). The development of reverse genetic and live mutant IBD vaccines as well as transgenic plants is of much interest and may be available to be used in the field in the near future.

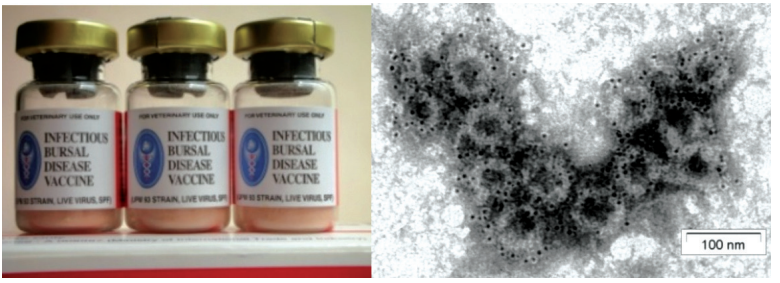
In addition various routes of vaccination and types of vaccine preparation, such as the immune complex vaccine used for *in ovo* or hatchery vaccination, could improve the efficacy of IBD vaccines (Hair-Bejo *et al,* 2000b). IBD vaccines also have high potential to be given via feed especially for free rearing or backyard chickens to ensure that they are free or protected against IBDV challenges (Hair-Bejo *et al*, 2004a). These groups of chickens can be a source of IBDV infection on commercial chickens and may complicate control and preventive measures for IBD outbreaks.

Control and Prevention of IBD

Control and prevention of IBD in chicken can be achieved in principle with proper vaccination programmes and biosecurity. Biosecurity encompasses management practices needed to prevent the spread of pathogens between farms and between buildings within a farm. Effective biosecurity to prevent the spread of the virus can be achieved with proper usage of disinfectants or, alternatively, electrochemical (ECA) products. It may be difficult and expensive to maintain a high level of biosecurity at all times. Thus, so far mechanisms involved in the defence againss IBD infections have been shown to involve pathways of immunological reactions. Proper flock health programmes should be practiced regularly at fixed times on a flock of chickens based on the epidemiology of the disease. The production performance as well as the feed and water intakes, mortality and morbidity rates, diagnosis of disease outbreak, vaccination responses and disease prevention should be monitored. The effectiveness of the programme should also be evaluated. The data should be analysed and evaluated intelligently in order to take the necessary actions for disease control and prevention. The control and prevention of diseases with characteristic clinical signs or symptoms, especially for those with high mortality, are relatively easy to achieve as these diseases are easy to recognise and diagnose, and cause direct impact on the health and production of the chickens. However, for the immunosuppressive diseases such as IBD, high mortality may not be observed during the initial stage of infection, but the performance of the affected chicken will be poor and they may die in the late stage of infection due to secondary infection by other pathogen/s (Hair-Bejo *et al.,* 2006b).

Development and Commercialisation of MyVAC UPM93 IBD Vaccine

In 2005, we successfully developed and commercialised a safe and effective MyVAC UPM93 IBD vaccine for chickens, specifically against vvIBDV field challenged. The vaccine's seed virus was novel and unique with molecular characteristics of the viral protein of the virus, having highly homology to vvIBDV field strains in Asia and Europe. This seed virus was isolated from the Poultry Farm, Universiti Putra Malaysia in 1993. The vaccine has passed all the laboratory tests required for dossier, such as tests for safety, sterility, back into virulent, virus titre and freedom from extraneous viruses. In 2004, field trials were conducted in commercial broiler chicken farms in Johor, Selangor and Perak, and it was proven that MyVAC UPM93 IBD is safe, effective and able to induce high and protective levels of IBD antibody even in chicken flocks with different levels of maternally derived antibody. The vaccine only caused mild to moderate bursal lesion with bursal recovery, without causing immunosuppression, interruption of body weight, FCR and performance of the chickens. Both the laboratory and field studies demonstrated that MyVAC UPM93 IBD vaccine is safe and effective in controlling and preventing vvIBDV field challenged in commercial chickens. The vaccine is currently available in the market and can be obtained from Malaysian Vaccines and Pharmaceutical Sdn Bhd. (Figures, 12 a, b).



(a) (b)

Figure 12 IBD vaccine innovation of UPM. (a) MyVAC UPM93, (b) Immunogold stained IBDV. TEM, Bar = 100nm.

The research and development (R&D) of MyVAC UPM93 IBD vaccine, prior to discussion on commercialisation potential with the vaccine companies, took about 8 years. Subsequently, just 5 years later, after agreement and completion of registration dossier and being approved by the authority, the vaccine was successfully launched for commercialisation in 2005.

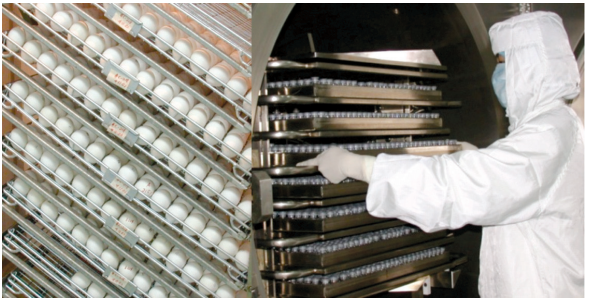
Briefly, the first stage of R&D involved IBDV isolation, identification and characterisation using both the conventional and molecular techniques. The isolates were propagated in the SPF embryonated chicken eggs and tissue cultures. The pathogenicity and immunogenicity of the isolates were determined in SPF and commercial chickens in the experimental house. The highly pathogenic isolates were selected for the challenge virus, whilst isolates with low pathogenicity and good immunogenicity were selected as potential candidates for the development of the IBD vaccine. Further, pathogenicity and immunogenicity tests were conducted for the isolates, prior to the final selection of the best isolate, one for vaccine development and the other for IBDV challenge virus.

A local isolate of IBDV, identified as UPM93, was selected from more than 20 vvIBDV of local isolate, adapted and successfully attenuated in SPF embryonated chicken eggs and tissue cultures for the development and production of the Malaysian IBD vaccine, MyVAC UPM93. The isolate showed low pathogenicity with good immunogenicity when inoculated in both the SPF and commercial chickens. The seed IBDV was prepared and tested to be free from any extraneous agents, other viruses, bacteria and mycoplasma, using both the conventional and molecular techniques.

The second stage of R&D involved study on the pathogenicity and immunogenicity of the IBD seed virus, in both SPF and commercial chickens under experimental conditions. The efficacy, safety, immunosuppressive effect, routes of vaccination and vaccination in SPF and commercial chickens were determined. A safe and effective IBD viral seed was successfully developed to confer protection against vvIBDV of field isolate, in both the SPF and commercial chickens under experimental conditions. The seed virus is effective to be used either via the intraocular, oral or *in ovo* route of vaccination. UPM 93 is highly immunogenic and able to neutralize high levels of IBD maternally derived antibody. It is able to confer full protection against vvIBDV field challenged, and is non immunosuppressive with mild bursal lesions and bursal recovery (Hair-Bejo, 2006b; Hair-Bejo *et al*., 2006a).

Market study was conducted prior to commercialisation and sale forecast determined (Ali *et al.,* 1988). Discussion with potential companies for commercialisation was conducted in 2000, and in 2001 the IBDV Master seed was handed over to the company for mass production of the IBD vaccine. The IBDV Mater seed virus was further tested for safety, efficacy, immunosuppressive and protective effects, minimum immunogenic dose and revision to virulence in SPF chickens. Briefly, the test demonstrated that the

Master seed is safe to be used in highly susceptible SPF White Leghorn chickens. It passed the purity and identity tests and freedom from extraneous agents, and proved for absence of revision to virulence following ten back passages of the working seed virus in SPF chickens. The vaccine is effective to confer full protection against vvIBDV challenged, safe and show bursal recovery. It does not interfere with ND vaccination. The shelf life of the vaccine is good and acceptable (Figures, 13a, b, c).



(a) (b)

(c)

Figure 13 MyVAC UPM93 IBD vaccine production in GMP Certified laboratory. (a) SPF embryonated chicken eggs inoculated with the virus, (b) Freeze drying of the vaccine, (c) Labeling of the vaccine.

A series of field trials were conducted in broiler farms in Johor, Selangor and Perak on the basis of their recent history of IBD or Gumboro outbreaks and as representatives of the Southern, Middle and Northern regions of the West Coast of Peninsular Malaysia, in 2004. The time of vaccination and management followed the common practice of the farms. The chickens in the control and vaccinated groups were challenged with vvIBDV. The study proved that MyVAC UPM93 IBD vaccine is effective in preventing further outbreaks of IBD in the flocks where the trials were held. It was a safe and efficacious vaccine under field conditions when used in flocks with either relatively low or high maternally derived antibody (MDA) to IBD and does not result in interference with the response to routine Newcastle disease vaccination. It induces antibody titre above the protective level (1000 ELISA unit) at 14 and 21 days post vaccination. The total percentages of mortality and FCR in the farms remained low throughout the trials (Figure, 14).

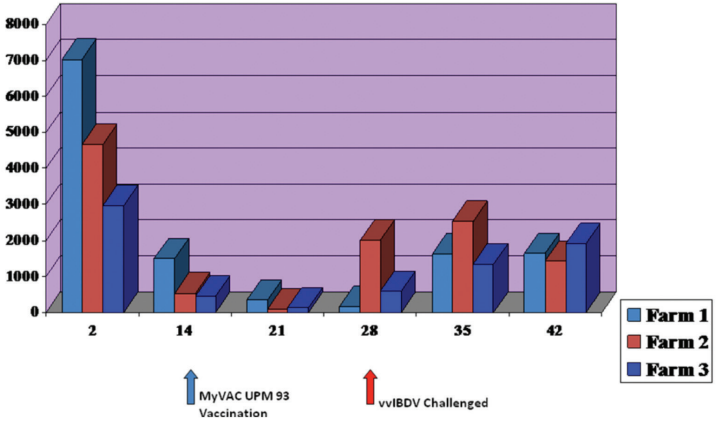


Figure 14 IBD antibody titre (ELISA unit). MyVAC UPM93 induced high antibody titre and provided full protection against vvIBDV, field challenged.

The vaccine was packaged and labeled. An instruction pamphlet was prepared to describe the composition and characteristics of the vaccine, methods of vaccination and dosage, storage conditions and precautions. The dossier were prepared and submitted for approval to the authority at the Department of Veterinary Services, Malaysia. Signing of Memorandum of Agreement between Universiti Putra Malaysia and Malaysian Vaccine and Pharmaceutical Sdn Bhd and launching of the vaccine for commercialization was held in September 2005. The study was supported by the government of Malaysia under the IRPA grant, during the 6, 7 and 8th Malaysia Plan, as part of the projects, and ITAF 2. In recognition of the innovation and achievements, MyVAC UPM93 IBD vaccine has been awarded "The Best Researcher Award on Commercialisation 2005, by UPM and the "National Research Innovation Award between Public and Private Sector 2008" by MOSTI (Figure, 15).

Figure 15 The National Research Innovation Award between Public and Private Sector 2008 by MOSTI in recognition of MyVAC UPM93 IBD vaccine innovation and achievements.

NEW GENERATION OF POULTRY VACCINES

Recombinant Vaccines

The virus proteins are expressed in bacteria, yeast, insects or mammalian cells. It is an alternative application using recombinant DNA technology for production of hybrid virus vaccines. The recombinant virus vaccine can multiply in infected cells, producing antigen of a wide range of virus. It is classified as live vector vaccines and naked DNA vaccines with no or low adverse side effects, relatively cheap, simple to produce, ease of administration, stable, adjuvant free and could confer protection against more than one antigen (insertion of one or more genes expressing immunogenic). Hybrid vaccines are stable and stimulate both cellular and humoral immunity (Shaw and Davison, 2000; Rogel, *et al.*, 2003; Pitcovski, *et al*., 2003; Nurulfiza, *et al*., 2006b; Phong, *et al,* 2007) .

Subunit Vaccines

Subunit vaccine consists of virus proteins that the immune system recognizes and makes antibodies for certain proteins on the virus and not the whole virus. Subunit vaccines may have great advantages over the conventional vaccines as it can be produced much faster and are safer than making vaccines using SPF embryonated chicken eggs. A subunit vaccine (synthetic peptide), consists of a single protein either purified from conventionally produced vaccine or produced by recombinant DNA technology. Peptide vaccines are a further reduction of subunit vaccines to minimal epitope required for induction of protection. Development depends on identification of the immunogenic site and hence is not applicable to all viruses, and do not readily stimulate T cells, thus requiring coupling to a protein carrier. However synthetic peptides vaccines are **c**hemically well defined, selective and safe, with no cold chain requirements

and thus can be cost effective and practical in tropical countries. The multi-mimotope protein r5EPIS promises to be a novel subunit vaccine candidate for IBDV (Wang, *et al.,* 2007).

DNA-based Vaccines

DNA-based vaccines consist of a segment of viral DNA and are different in structure from conventional vaccines. They consist of plasmids, small rings of double-stranded DNA originally derived from bacteria, totally unable to produce an infection. The plasmids used for immunization have been altered to carry genes specifying one or more antigenic proteins, normally made by a selected pathogen. When it is injected into the body, the artificial DNA is taken up by cells, which translate the DNA into viral proteins. This triggers the immune system to produce antibodies for the viral proteins, therefore providing protection against infection. DNA-based vaccine is relatively cheap, fast to produce, stable to store and will never be able to cause infection. The vaccine could be given using an air gun, by shooting a tiny DNA-covered particle under the skin (Jalilian, *et al.,* 2010; Lim, *et al.,* 2008).

Reverse Genetics

A mutant viral vaccine, which lacks a specific gene encoding a highly immunogenic protein, is useful in eradication programmes as it allows differentiation between the infected and vaccinated chickens (DIVA vaccines). Genetic vaccines are capable of eliciting humoral and cellular immunity, are safe, fast to develop, stable and easy to formulate into multivalent vaccines (Noue¨n, *et al*., 2006; Moura, *et al*., 2007).

Transgenic Plant Vaccines

A novel method of vaccination based on convenience of oral immunization. It eliminates the need for trained staff for vaccine administration, cold chain storage, transportation, cost of syringes and very practical in free rearing of chickens. The expression level of VP2 protein of IBDV in transgenic rice seeds varied from 0.678 % to 4.521 % μg/mg of the total soluble seed protein (Wu *et al.,* 2007).

CONCLUSIONS

The success of the poultry industry in the country and worldwide depends to a significant degree on the health and production of the chickens. The threat of infectious diseases, either emerging or reemerging diseases, will continue in the industry and thus poultry vaccines are powerful tools in disease control and prevention. R&D are important elements in the industry and innovation to produce a safe and effective vaccine, either the conventional or new generation of poultry vaccines which is also cheap, efficient and better, is the priority in any vaccine development and production. This can be achieved through advanced knowledge in animal biotechnology and molecular biology. However, only a small percentage of inventions from R&D end up in commercialisation especially in developing countries like Malaysia. The lack of local and international manufacturing companies based in the country could explain this failure. Furthermore, it will be only economical and cost effective if the company, as well as the product, is able to compete not only in the local market, but also internationally.

It appears that conventional vaccines will still be the major vaccine produced in the near future, but new generation vaccines hold promise of more advantages ahead although there is a big horizon to explore before this becomes a reality. Poultry vaccines

not only protect chickens from death or poor performance, but also reduce or prevent the use of antibiotics and other toxic chemicals and thus ensure the safety and quality of chicken products. The poultry industry is an excellent model for the livestock industry in the country with annual growth of about 5.95%, 100% self sufficiency and with about 15% of total production exported. This achievement must be sustained and further improved in line with NAP3 and NEM through proper disease control and vaccination programmes.

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BIOGRAPHY

Prof Dr Mohd Hair bin Bejo was born on 1 May 1960 in Muar, Johor. He received his formal education in Sekolah Kebangsaan Parit Latiff, Muar and secondary education in Sekolah Menengah Semerah and High School, Batu Pahat, Johor. In 1985, he obtained his Doctor of Veterinary Medicine (DVM) from Universiti Putra Malaysia (UPM). He furthered his study at the University of Liverpool England in 1987 and obtained his PhD in the field of Veterinary Pathology three years later. In 1993, he did his post-doctorate training in the field of Avian Pathology at the University of Georgia, Athens, USA.

Prof Hair-Bejo was appointed as a lecturer in Veterinary Pathology in the Department of Veterinary Pathology and Microbiology, Faculty of Veterinary Medicine, UPM in January 1991 and was later promoted as an Associate Professor and a Professor in November 1999 and October 2007, respectively. In February 2002, he was appointed as the Head of Department of Veterinary Pathology and Microbiology, and 9 months later in November 2002 he was offered the position as Deputy Dean (Research and Post-graduate Studies), Faculty of Veterinary Medicine, UPM, an administrative position that he currently holds. He has had the opportunity to lead four main sections of the Faculty: research, post-graduate studies, consultancy and continuing education and implement the Management Quality System ISO 9001:2000 which was awarded in July 2000.

Other than that, Prof Hair-Bejo has been actively involved in teaching, research and professional services, particularly in the field of veterinary and avian pathology, and animal biotechnology. He has taught courses in veterinary pathology, and avian pathology and diseases for both undergraduate and post graduate students. He had supervised 42 PhD students, 43 Masters students and 43

undergraduate students in their final year projects. He has been appointed as an Examiner and Chairman of the Examination Committee for PhD and Masters Theses. He has also been appointed as a member of various examination boards such as comprehensive examination and animal industry project seminar for the DVM programme, applied animal science for Diploma in Animal Health and Production (DKHP) programme and training certificate for veterinary assistance in the Department of Veterinary Services, Malaysia.

Besides that, Prof Hair-Bejo procured funds and was the project leader for 10 research projects and as a team member for 15 other projects. In addition, he had also been involved in collaborative research with 8 companies of the related industries. He was also actively involved as a member of various research committees such as Panel of the Technical Committee, Agro-Industrial Sector for Research IRPA Grant under RMK 8, Panel of Assessment for Fundamental Research Grant Scheme (FRGS), Science Fund, TechnoFund and Research University Grant Scheme (RUGS).

In September 2005, Prof Hair-Bejo successfully commercialised his research product namely MyVAC UPM93 Infectious Bursal Disease Vaccine for Malaysian and Asian market. Recently, he has completed his pre-commercialisation research project in collaboration with an industry under TechnoFund scheme on Anolyte products for the production of safe and healthy chickens and to be used as disinfectants for biosecurity. Prof Hair-Bejo has also just received a new TechnoFund grant for the pre-commercialisation of MyVAC UPM81 tissue culture based on infectious bursal disease vaccine. He is known to be actively involved in the production of new generation of vaccines and latest technology in vaccine production. Prof Hair-Bejo is currently looking for suitable partners for up-scaling and commercialisation of his 3 ELISA kits and 1

Real-Time PCR kit for infectious bursa disease (IBD), and palm kernel cake dietary formulation for ruminants. He has won 12 gold, 10 silver and 6 bronze medals, and was awarded as the best oral (twice) and poster (4 times) presentations. He has submitted 3 applications for patent filed for his research products on IBD in United States, European and Malaysia Patent and Trademark Offices.

Prof Hair-Bejo has an excellent record of publications from his research findings. He has published 70 papers in refereed journals, 4 articles as chapter in books, 210 papers in proceedings, 100 in other forms of publications and 60 without proceedings locally and internationally. He has also presented his work as an invited speaker and at international meetings such as in United Kingdom, France, Hungary, United States of America, Australia, China, Japan, Korea, Turkey, Iran, Bangladesh, Cambodia, Thailand, Indonesia and Singapore. He was the Editor-in-Chief for Jurnal Veterinar Malaysia. He is currently, the Editor, a member of the Editorial Board and a reviewer for the Malaysian Journal of Microscopy, the Malaysian Journal of Animal Science and the Journal of Tropical Agricultural Science, respectively as well as the Editor and a member of the Editorial Committee for a few seminars, conferences, proceedings, and newsletters.

Prof Hair-Bejo is a practicing veterinary pathologist and is actively involved in diagnostic work and provides advisory services for cases from the university, government agencies, research institutes and industries. He was the coordinator for Post Mortem Laboratory from 1991 to 2002 and the Manager of the Veterinary Laboratory Services Unit in 1997 to 1998 prior to the merging of the unit to the University Veterinary Hospital.

Prof Hair-Bejo is currently the Treasurer of Asian Association of Veterinary School (AAVS), the Secretary of South East Asia

Veterinary School (SEAVS) and a member of the Executive Committee of the World's Poultry Science Association (WPSA) Malaysian Branch. He is the Former President of Malaysian Society of Animal Production (MSAP) and a member of the Executive Committee of the Asian-Australasian Association of Animal Production (AAAP) Societies. He is actively involved in electron microscopy and was appointed President of Electron Microscopy Society Malaysia (EMSM) for 5 consecutive years. He was also a member of the Executive Committee of the Asia Pacific Societies of Electron Microscopy (CAPSEM) and the ASEAN Microscopy Society. In addition, he was a member of the Executive Committee of the International Advisory Board, and a member as well during the 8th Asia-Pacific Electron Microscopy (APEM) Conference besides being the Secretary of the 11th International Conference of the Association of Institutions for Tropical Veterinary Medicine (CAITVM). He has also served as President of the Association of Educators in Veterinary Sciences (EDUVET) Malaysia, and the Social and Recreational Club, Faculty of Veterinary Medicine (KSRV), UPM, as well as held other positions such as vice president, secretary, treasurer, auditor and member of various societies locally and internationally.

Prof Hair-Bejo has achieved excellence in teaching, research, professional services, administration and leadership nationally and internationally. He has the resilience and confidence for bigger roles ahead to contribute towards advancement and discovery of new knowledge, wealth creation, and a caring and loving society.

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Tan Sheau Wei ● Mrs Taherian Mozhdeh ● Mrs Mozhgan Mollayee ● Mr Wan Keng Fei.

Masters: ● Dr Almenesh Woldeyes Yimer ● Dr Roosevien Farida Nilawati Rachmat ● Dr Karuna Sharma ● Dr Thu Zar Than @ Hafiza Hashim ● Dr Ahmad S Farag ● Mr Kenny Voon Goh Leong ● Mrs Khor Sok Fang ● Mr Jason Pal Singh Kipra ● Mr Mohd Hakimi Ahmad Zainudin ● Dr Tesfaheywet Zeryehun Shiferaw ● Dr Ayalew Berhanu Mekonnen ● Mr Anyanji Victor Uchenna ● Mrs Atefeh Sheikhlar ● Dr Anun Man ● Dr Bala Ram Thapa ● Mr Babak Jalilian ● Mr Cheng Xiang Feng ● Mrs Hairul Aini Hamzah ● Dr Hareth Yahya Ahmed Shujaaedin ● Ms Intan Shazlin Tajul Ashikin ● Ms Juliana Mohd Ayob ● Dr Farhana Yasmin ● Ms Li Juan ● Dr Liew Pit Kang ● Ms Mahsa Moteshakeri ● Mr Mehdi Javadi ● Mr Moslarikiman Ismail ● Mrs Mahanom Hussin ● Dr Marina Hassan ● Mr Moslarikiman Ismail ● Dr Mustafa Fadhil Mohammad ● Dr Mohammad Reza Taherian ● Mrs Rafidah Saadun ● Mr Riyadh Abbas Abdo Al-Kirshi ● Ms Noraina Muhamad Zakuan ● Mr Nguyen Tien Thanh ● Mr Saeed Sharif ● Mrs Sairah Abdul Karim ● Ms Siti Hasmah Mohtar ● Mrs Suhaidah Ibrahim ● Dr Tan Ching Giap ● Dr Zerihun Hailemariam Negasi ● Dr Zahraa F A Al-Barghash ● Mr Zhou Xiaoli ● Mr Zulkefley Othman.

Undergraduate Final Year Project: ● Dr Hass Md Yatim ● Dr Lim Wan Siam ● Dr Ooi Peck Toung ● Dr Ng Mun Kin ● Dr Poo Vern Ying ● Dr Ng Hon Yean ● Dr Chan Kok Kiong ● Dr Choo Ooi Hiong ● Dr Chua Pei Lin ● Dr Julaida Sulaiman ● Dr Juliyana Abu Sari ● Dr Kerr Ai Ru ● Dr Khalilah Khalil ● Dr Lee Chan Ling ● Dr Lee Choon Shen ● Dr Lee Ee Teik ● Dr Leong Kah Weng ● Dr Maria Jamli ● Dr Mardiyah M Nasir ● Dr Maria Goretti Tirant ● Dr Mohd Faizal Ghazali ● Dr Mas Ayu Suraya Abdul Rahman ● Dr Mohd Fuad Matori ● Dr Natrah Abd Razak ● Dr Nik Mohd Faiz Nik Mohd Azmi ● Dr Norazian Abdul Hamid ● Dr Phang Wai San ● Dr Phong

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LIST OF INAUGURAL LECTURES

1. Prof. Dr. Sulaiman M. Yassin
   The Challenge to Communication Research in Extension
   22 July 1989

2. Prof. Ir. Abang Abdullah Abang Ali
   Indigenous Materials and Technology for Low Cost Housing
   30 August 1990

3. Prof. Dr. Abdul Rahman Abdul Razak
   Plant Parasitic Nematodes, Lesser Known Pests of Agricultural Crops
   30 January 1993

4. Prof. Dr. Mohamed Suleiman
   Numerical Solution of Ordinary Differential Equations: A Historical Perspective
   11 December 1993

5. Prof. Dr. Mohd. Ariff Hussein
   Changing Roles of Agricultural Economics
   5 March 1994

6. Prof. Dr. Mohd. Ismail Ahmad
   Marketing Management: Prospects and Challenges for Agriculture
   6 April 1994

7. Prof. Dr. Mohamed Mahyuddin Mohd. Dahan
   The Changing Demand for Livestock Products
   20 April 1994

8. Prof. Dr. Ruth Kiew
   Plant Taxonomy, Biodiversity and Conservation
   11 May 1994

9. Prof. Ir. Dr. Mohd. Zohadie Bardaie
   Engineering Technological Developments Propelling Agriculture into the 21st Century
   28 May 1994

10. Prof. Dr. Shamsuddin Jusop
    Rock, Mineral and Soil
    18 June 1994

11. Prof. Dr. Abdul Salam Abdullah
Natural Toxicants Affecting Animal Health and Production
29 June 1994

12. Prof. Dr. Mohd. Yusof Hussein
Pest Control: A Challenge in Applied Ecology
9 July 1994

13. Prof. Dr. Kapt. Mohd. Ibrahim Haji Mohamed
Managing Challenges in Fisheries Development through Science and Technology
23 July 1994

14. Prof. Dr. Hj. Amat Juhari Moain
Sejarah Keagungan Bahasa Melayu
6 Ogos 1994

15. Prof. Dr. Law Ah Theem
Oil Pollution in the Malaysian Seas
24 September 1994

16. Prof. Dr. Md. Nordin Hj. Lajis
Fine Chemicals from Biological Resources: The Wealth from Nature
21 January 1995

17. Prof. Dr. Sheikh Omar Abdul Rahman
Health, Disease and Death in Creatures Great and Small
25 February 1995

18. Prof. Dr. Mohamed Shariff Mohamed Din
Fish Health: An Odyssey through the Asia - Pacific Region
25 March 1995

19. Prof. Dr. Tengku Azmi Tengku Ibrahim
Chromosome Distribution and Production Performance of Water Buffaloes
6 May 1995

20. Prof. Dr. Abdul Hamid Mahmood
Bahasa Melayu sebagai Bahasa Ilmu- Cabaran dan Harapan
10 Jun 1995

21. Prof. Dr. Rahim Md. Sail
Extension Education for Industrialising Malaysia: Trends, Priorities and Emerging Issues
22 July 1995

22. Prof. Dr. Nik Muhammad Nik Abd. Majid
The Diminishing Tropical Rain Forest: Causes, Symptoms and Cure
19 August 1995

23. Prof. Dr. Ang Kok Jee
The Evolution of an Environmentally Friendly Hatchery Technology for Udang Galah, the King of Freshwater Prawns and a Glimpse into the Future of Aquaculture in the 21st Century
14 October 1995

24. Prof. Dr. Sharifuddin Haji Abdul Hamid
Management of Highly Weathered Acid Soils for Sustainable Crop Production
28 October 1995

25. Prof. Dr. Yu Swee Yean
Fish Processing and Preservation: Recent Advances and Future Directions
9 December 1995

26. Prof. Dr. Rosli Mohamad
Pesticide Usage: Concern and Options
10 February 1996

27. Prof. Dr. Mohamed Ismail Abdul Karim
Microbial Fermentation and Utilization of Agricultural Bioresources and Wastes in Malaysia
2 March 1996

28. Prof. Dr. Wan Sulaiman Wan Harun
Soil Physics: From Glass Beads to Precision Agriculture
16 March 1996

29. Prof. Dr. Abdul Aziz Abdul Rahman
Sustained Growth and Sustainable Development: Is there a Trade-Off 1 or Malaysia
13 April 1996

30. Prof. Dr. Chew Tek Ann
Sharecropping in Perfectly Competitive Markets: A Contradiction in Terms
27 April 1996

31. Prof. Dr. Mohd. Yusuf Sulaiman
Back to the Future with the Sun
18 May 1996

32. Prof. Dr. Abu Bakar Salleh
Enzyme Technology: The Basis for Biotechnological Development
8 June 1996

33. Prof. Dr. Kamel Ariffin Mohd. Atan
The Fascinating Numbers
29 June 1996

34. Prof. Dr. Ho Yin Wan
Fungi: Friends or Foes
27 July 1996

35. Prof. Dr. Tan Soon Guan
Genetic Diversity of Some Southeast Asian Animals: Of Buffaloes and Goats and Fishes Too
10 August 1996

36. Prof. Dr. Nazaruddin Mohd. Jali
Will Rural Sociology Remain Relevant in the 21st Century?
21 September 1996

37. Prof. Dr. Abdul Rani Bahaman
Leptospirosis-A Model for Epidemiology, Diagnosis and Control of Infectious Diseases
16 November 1996

38. Prof. Dr. Marziah Mahmood
Plant Biotechnology - Strategies for Commercialization
21 December 1996

39. Prof. Dr. Ishak Hj. Omar
Market Relationships in the Malaysian Fish Trade: Theory and Application
22 March 1997

40. Prof. Dr. Suhaila Mohamad
Food and Its Healing Power
12 April 1997

41. Prof. Dr. Malay Raj Mukerjee
A Distributed Collaborative Environment for Distance Learning Applications
17 June 1998

42. Prof. Dr. Wong Kai Choo
Advancing the Fruit Industry in Malaysia: A Need to Shift Research Emphasis
15 May 1999

43. Prof. Dr. Aini Ideris
Avian Respiratory and Immunosuppressive Diseases- A Fatal Attraction
10 July 1999

44. Prof. Dr. Sariah Meon
Biological Control of Plant Pathogens: Harnessing the Richness of Microbial Diversity
14 August 1999

45. Prof. Dr. Azizah Hashim
The Endomycorrhiza: A Futile Investment?
23 Oktober 1999

46. Prof. Dr. Noraini Abdul Samad
Molecular Plant Virology: The Way Forward
2 February 2000

47. Prof. Dr. Muhamad Awang
Do We Have Enough Clean Air to Breathe?
7 April 2000

48. Prof. Dr. Lee Chnoong Kheng
Green Environment, Clean Power
24 June 2000

49. Prof. Dr. Mohd. Ghazali Mohayidin
Managing Change in the Agriculture Sector: The Need for Innovative Educational Initiatives
12 January 2002

50. Prof. Dr. Fatimah Mohd. Arshad
Analisis Pemasaran Pertanian di Malaysia: Keperluan Agenda Pembaharuan
26 Januari 2002

51. Prof. Dr. Nik Mustapha R. Abdullah
Fisheries Co-Management: An Institutional Innovation Towards Sustainable Fisheries Industry
28 February 2002

52. Prof. Dr. Gulam Rusul Rahmat Ali
Food Safety: Perspectives and Challenges
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