IMMUNOGENICITY AND EFFICACY OF INFECTIOUS BURSAL DISEASE VIRUS (IBDV) VACCINES AGAINST THE MALAYSIAN VARIANT IBDV IN BROILER CHICKENS

By

PANIZ ZARGHAMI DASTJERDI

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

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IB 2024 2

DEDICATION

To my beloved parents Hamidreza and Saffieh, and my grandmother, Gohar
May God bless them with joy, peace, and happiness.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

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Chairman : Professor Abdul Rahman bin Omar, PhD
Institute : Bioscience

Infectious bursal disease (IBD) (Gumboro disease) is a viral disease in young chickens that causes immunosuppression. It is caused by the infectious bursal disease virus (IBDV), a highly resistant non-enveloped RNA virus. Effective disease control and prevention strategies focus on farm biosecurity and vaccination. However, the emergence of novel variant IBDV (nvarIBDV) has challenged vaccine efficacy. An improved version of the herpesvirus of turkey (HVT) vector vaccine, HVT+IBD+ND, has been developed recently. However, the efficacy of IBDV vaccines has not been evaluated against the emerging Malaysian variant of IBDV in commercial broiler chickens. This study evaluated the immunogenicity and efficacy of live attenuated and viral vector vaccines against variant IBDV in chickens.

In the immunogenicity study, ELISA method was used to detect antibody titers. The HVT+IBD group had a higher mean antibody titer compared to the

HVT+IBD+ND group, as detected by the VP2 IBDV-specific ELISA (p<0.05) in the broiler chickens at 28 days old. Both vaccinated groups showed low bursal lesion scores. As expected, antibody titers were detectable by the VP2 IBDV-specific ELISA but not with the whole IBDV-specific ELISA. Real-time qPCR showed a significantly higher HVT load in the HVT+IBD group (p<0.05). Upon comparison with the IBD-BLEN, it seems that the IBD-BLEN vaccine generates a high mean antibody titer (1623.00 ± 2031.13 and 4775.00 ± 3418.77) as detected by whole IBDV and VP2 IBDV-specific ELISA, respectively, however, it is associated with a high bursal lesion score of 3.0 at 28-day-old chickens.

The efficacy of the HVT-based vaccine against the nvarIBDV strain UPM1432/2019 was evaluated. The HVT+IBD vaccine and HVT+IBD+ND vaccinated birds have seroconversion rates against IBD of 97% and 32.5%, respectively. However, both groups had bursal lesions following challenged with nvarIBDV. The HVT+IBD group had a higher mean antibody titer (7168 ± 3753.26), and less bursal damage at day 7 and 14 post-challenge compared to HVT+IBD+ND (1209.1 ± 1252.88) (p<0.05), indicating the HVT+IBD vaccine offers partial protection against nvarIBDV challenge. In addition, the HVT+IBD group had a statistically higher normalized HVT value in the bursa and spleen than the HVT+IBD+ND group (p<0.05). Although the HVT loads were higher for HVT+IBD (p<0.05), variant IBDV loads were similar between groups post-challenge ($p > 0.05$), indicating the vaccines could not induce virus clearance.

The immunosuppression study showed variant IBDV challenge could inhibit the antibody response after Newcastle disease (ND) vaccination in broiler chickens with a significant reduction at day 14 post-challenge (1493.0 ± 746.1) ($p < 0.05$) but not at day 7 ($p > 0.05$). In conclusion, the current HVT-based vaccines against IBD cannot provide complete protection against the Malaysian variant IBDV infection in commercial broiler chickens. In addition, infection with variant IBDV can suppress the production of antibodies following ND vaccination. Findings from this study recommend implementing new strategies, including the use of variant IBD vaccine in controlling variant IBDV and its immunosuppression effect in broiler chickens.

Keywords: Infectious Bursal Disease Virus, Gumboro disease, Broiler chicken, Vector Vaccine, Live attenuated vaccine

SDG: GOAL 3: Good Health and Well-Being

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

MENILAI VIRAL "VIRUS PENYAKIT BURSAL BERJANGKATAN BERASASKAN VECTOR (IBDV) VAKSIN IMUNOGENISITI DAN KEBERKESANAN TERHADAP IBDV VARIAN MALAYSIA DALAM AYAM BROILER KOMERSIL

Oleh

PANIZ ZARGHAMI DASTJERDI

Ogos 2024

Pengerusi : Profesor Abdul Rahman bin Omar, PhD
Institut : Biosains

Penyakit bursal berjangkit (IBD) (Penyakit Gumboro) adalah penyakit virus yang menjejaskan anak ayam dan menyebabkan pengimunotindasan. Penyakit ini disebabkan oleh virus penyakit bursal berjangkit (IBDV), sejenis virus RNA tidak bersampul yang sangat tahan, justeru, strategi kawalan dan pencegahan penyakit yang berkesan adalah berdasarkan biosekuriti ladang dan vaksinasi. Walau bagaimanapun, prestasi vaksin IBDV boleh terjejas disebabkan oleh kemunculan baru-baru ini varian antigenik baru IBDV. Baru-baru ini, versi vaksin vektor herpesvirus ayam belanda (HVT) yang lebih baik, HVT+IBD+ND, telah dibangunkan. Walau bagaimanapun, keberkesanan vaksin IBDV ini belum dinilai terhadap IBDV varian Malaysia dalam ayam pedaging komersial.

Dalam kajian imunogenisiti, keadah ELISA digunakan untuk mengesan titer antibodi. Kumpulan yang divaksin HVT+IBD mempunyai titer antibodi purata

yang lebih tinggi berbanding kumpulan HVT+IBD+ND seperti yang dikesan oleh ELISA khusus VP2 IBDV ($p<0.05$) dalam ayam pedaging pada umur 28 hari. Kedua-dua kumpulan yang divaksin menunjukkan skor lesi bursal yang rendah. Seperti yang dijangkakan, titer antibodi hanya boleh dikesan menggunakan ELISA khusus VP2 IBDV tetapi tidak dengan ELISA keseluruhan khusus IBDV. Di samping itu, pengesanan qPCR masa nyata beban HVT adalah lebih tinggi dalam kumpulan HVT+IBD berbanding kumpulan HVT+IBD+ND ($p<0.05$). Jika dibandingkan dengan vaksin hidup yang dilemahkan, nampaknya vaksin IBD-BLEN menghasilkan titer antibodi purata yang tinggi iaitu 1623.00 ± 2031.13 dan 4775.00 ± 3418.77 seperti yang dikesan oleh ELISA keseluruhan khusus IBDV dan ELISA khusus VP2 IBDV, masing-masing, bagaimanapun ia dikaitkan dengan skor lesi bursal yang tinggi iaitu 3.0 dalam ayam pedaging pada umur 28 hari.

Keberkesanan vaksin HVT+IBD dan HVT+IBD+ND terhadap nvarIBDV strain UPM1432/2019 telah dinilai. Vaksin HVT+IBD dan HVT+IBD+ND mempunyai kadar penukaran serum terhadap IBD, 97% dan 32.5%, masing-masing. Walau bagaimanapun, berikutan cabaran dengan IBDV varian, kedua-dua kumpulan yang diberi vaksin mengalami kerosakan bursa. Kumpulan HVT+IBD yang mempunyai purata titer antibodi yang tinggi (7168 ± 3753.26), diterjemahkan kepada kurang kerosakan bursa pada hari ke-7 dan 14 selepas cabaran (pc) berbanding HVT+IBD+ND, yang mempunyai titer antibodi purata yang rendah (1209.1 ± 1252.88) ($p<0.05$), menunjukkan vaksin HVT+IBD menawarkan perlindungan separa terhadap cabaran IBDV varian. Di samping itu, kumpulan HVT+IBD mempunyai nilai HVT ternormal yang lebih tinggi

secara signifikan dalam bursa dan limpa berbanding kumpulan HVT+IBD+ND ($p<0.05$). Walau bagaimanapun, beban HVT untuk HVT+IBD ($p<0.05$) adalah tinggi, beban IBDV varian adalah sama di antara kumpulam selepas cabaran ($p >0.05$), menunjukkan ketidakupayaan vakisn untuk mengaruh pembersihan virus.

Kajian pengimunotindasan mendedahkan bahawa cabaran IBDV varian boleh menindas tindak balas antibodi berikutan vaksinasi penyakit Newcastle (ND) dalam ayam daging, dengan pengurangan signifikan titer antibodi ND pada hari 14 pc (1493.0 ± 746.1) ($p<0.05$) tetapi tidak pada hari 7 pc (2309.1 ± 1034.4) ($p >0.05$) berbanding kumpulan ND yang tidak dicabar (2975.7 ± 189.5). Kesimpulannya, vaksin berasaskan HVT semasa terhadap IBD tidak dapat memberikan perlindungan sepenuhnya terhadap jangkitan IBDV varian Malaysia dalam ayam pedaging komersial. Di samping itu, jangkitan dengan IBDV varian boleh menyekat pengeluaran antibodi berikutan vaksinasi ND. Penemuan daripada kajian ini menyarankan penggunan strategi baharu, termasuk penggunaan vaksin IBD varian dalam mengawal varian IBDV dan kesan pengimunotindasan dalam ayam pedaging.

Kata Kunci: Virus Penyakit Bursal Berjangkit, Penyakit Gumboro, Ayam pedaging, Vaksin Vektor, Vaksin hidup dilemahkan

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Abdul Rahman bin Omar, PhD
Professor
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Chairman)

Mohd Hair Bejo, PhD
Professor
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Member)

Nor Yasmin Abd Rahman, PhD
Assistant professor
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Member)

Nik Mohd Faiz Nik Mohd Azmi, PhD
Assistant Professor
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Member)

ZALILAH MOHD SHARIFF, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

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aa	Amino acid
ANOVA	Analysis of variance
APC	Antigen presenting cell
B	Base
BBW	Bursal to body weight ratio
BF	Bursa of Fabricius
BLAST	Basic local alignment search tools
BLS	Bursal lesion score
bp	Base pair
CAM	Chorioallantoic membrane
ChIL	Chicken interleukin
CMI	Cell-mediated immunity
Cq	Quantification cycle
CTL	Cytotoxic T cell
cvIBDV	Classical virulent infectious bursal disease virus
dIBDV	Distinct infectious bursal disease virus
DIVA	Differentiation of infected versus vaccinated animals
DNA	Deoxyribonucleic acid
dpc	Days post challenge
dpi	Days post infection
dpv	Days post vaccination
dsRNA	Double-stranded RNA
E	Efficiency
EDTA	Ethylene-diamine-tetraacetic-acid
EID_{50}	Median egg infectious dose

ELISA	Enzyme-linked immunosorbent assay
HVR	Hypervariable region
HVT	Herpesvirus of turkey
IBD	Infectious bursal disease
IBDV	Infectious bursal disease virus
Icx	Immune complex
Ig	Immunoglobulin
IgM	Immunoglobulin M
IL	Interleukin
iNOS	Inducible nitric oxide synthetase
LAMP	Loop-mediated isothermal amplification
Mab	Monoclonal antibody
MDA	Maternally derived antibody
MHC	Major histocompatibility complex
mL	Millilitre
mRNA	Messenger ribonucleic acid
NDV	Newcastle disease virus
NF-kB	Nuclear factor kappa enhancer binding protein
ng/µL	Nanogram per microlitre
NGS	Next-generation sequencing
NK	Natural killer
ºC	Degree Celsius
OIE	Office International des Epizooties
ORF	Open reading frame
PP	Polyprotein
R2	Coefficient of correlation

RdRp	RNA-dependent RNA polymerase
RT	Reverse-transcription
RT-PCR	Reverse-transcription polymerase chain reaction
RT-qPCR	Quantitative reverse-transcription polymerase chain reaction
SBW	Spleen to body weight ratio
SPF	Specific-pathogen-free
Th1	T helper cell 1
Th2	T helper cell 2
TLR	Toll-like receptor
Tm	Melting temperature
UPM	Universiti Putra Malaysia
UTR	Untranslated region
v/v	Volume by volume
vaIBDV	Variant infectious bursal disease virus
VDAC2	Voltage-dependent anion channel 2
VN	Virus neutralization
VP	Viral protein
VRI	Veterinary Research Institute
vRNA	Viral RNA
vvIBDV	Very virulent infectious bursal disease virus
WOAH	World Organisation for Animal Health
w/v	Weight per volume
%	Percent
µg	Microgram
µL	Microlitre
α	Alpha

β	Beta
γ	Gamma

CHAPTER 1

INTRODUCTION

1.1 Background of the Study

A recent study indicated that poultry production in Asia contributed 40% of global meat production in 2023 (Day, 2023; Mahanty et al., 2023), providing sufficient and healthy numbers of eggs and chickens for the growing world population. A recent survey indicated each Malaysian consumed 48.32kg of chicken in a year (Statica, 2023), emphasizing the importance of the poultry industry in this region. However, the poultry industry faces numerous challenges, such as increases in feed prices, animal welfare regulation, and the increasing cost of disease prevention and farm management (Shaban & Alabboodi, 2019).

Pathogenic viruses have always posed a huge risk to poultry farms, as they can cause death or indirectly cause secondary infections, thus increasing the costs of production. Infectious bursal disease (IBD) (Gumboro disease) is one of these acute viral diseases affecting young chickens caused by infectious bursal disease virus (IBDV), a single-shelled, non-enveloped, double-stranded (ds) RNA virus from the family Birnaviridae of the genus Avibirnavirus (Hudson et al., 1986). IBDV has a predilection for the cells of the bursa of Fabricius where the virus infects actively dividing and differentiating lymphocytes of the B-cell lineage (Nagarajan & Kibenge, 1997)

The first outbreak of IBD was reported in commercial chicken flocks in Delaware, USA (Cosgrove, 1962). The IBDV strains, which were isolated during this outbreak, are now known as classical serotype I isolates. Based on antigenic variation and virulence, IBDV can be divided into several groups: classical virulent, attenuated strains consisting of primarily vaccine strains, antigenic variants, and very virulent (vv) strains (Cao et al., 1998). The disease can cause significant economic losses due to immunosuppression and high mortality rates even up to 90% in susceptible chickens infected with a vv strain of IBDV. The antigenic variants of IBDV isolates were first detected in the USA in the 1980s (Marel et al., 1990). This variant strain emerged from flocks with selection pressure of field vaccination against classical IBDV serotype I, with changes occurring at the hypervariable region of the VP2 gene responsible for inducing virus-neutralizing antibodies (Wang et al., 2019).

IBDV was first reported in Malaysia in 1991 (Hair-Bejo et al., 1991) and was associated with vvIBDV. Likewise, vvIBDV has been detected in many Asian countries and has remained the leading IBD in commercial poultry flocks (Dey et al., 2019a). However, several Asian countries recently detected the emergence of a novel variant IBDV (Fan et al., 2019; Y. Huang et al., 2023; Lian et al., 2021; Thai et al., 2021; Jiang, et al., 2021; Yamazaki et al., 2017). Sequence analysis showed the Asian variant IBDV is grouped with the variant IBDV from the USA in genogroup 2, while the vvIBDV and the classical IBDV have been grouped under genogroup 3 and 1, respectively (Michel & Jackwood, 2017).

Aliyu et al. first reported the detection of a novel variant in Malaysia in commercial broiler flocks vaccinated against IBD with the classical IBDV vaccine. The Malaysian variant IBDV is highly genetically comparable to the novel Chinese variants, and they have high similarity (Aliyu et al., 2021). Subsequent studies indicated novel variant IBDV can cause bursal atrophy and immunosuppression causing vaccine failures and increasing the risk of secondary infections (Fan, Wu, et al., 2020; Y. Huang et al., 2023; Lian et al., 2021a).

Diagnosis of IBD is based on post-mortem examination and isolation and identification of the virus based on embryonated chicken egg inoculation and PCR detection of the virus (Barlič-Maganja et al., 2002). Besides detecting the virus antigen, serology assays, namely agar gel precipitin (AGP), enzyme-linked immunosorbent assay (ELISA), and viral neutralization test (Dey et al., 2019a) can be used to detect the virus and to measure the antibody titer for profiling following vaccination. Presently, ELISA has been widely used to measure the antibody titer following IBD vaccination in commercial poultry flocks (Marquardt et al., 1980). In ELISA, the detection of specific antibodies to IBDV uses the whole viral particle or partial VP2 protein as the antigen. (Prandini et al., 2016; Sedeik et al., 2019).

Control and prevention of IBD rely on strict farm biosecurity and vaccination since the virus is highly resistant and can persist in the environment for up to 122 days (Barzon et al., 2013). The use of appropriate vaccine types and combinations can induce effective protection (Müller et al., 2012). Different

types of vaccines have been developed since the 1980s against the vvIBDV and, essentially, against the antigenic variants (Mundt et al., 2003). The live attenuated vaccinated are the most common vaccines, and are mostly developed from classical virulent strains and may display low efficiency due to interference of MDA and the emergence of variant IBDV (Jackwood & Saif, 1987) and vvIBDV (Chettle et al., 1989).

Intermediate and intermediate plus vaccines have better efficacies and are effective in controlling vvIBDV but can cause moderate to severe bursal damage (Camilotti et al., 2016; Rautenschlein et al., 2002; Sedeik et al., 2019). The other type of vaccine is the killed IBD vaccine, water-in-oil emulsion preparations with antigens. Most breeder flocks get these vaccines to pass the immunity to the offspring (Liu et al., 2018). Besides conventional IBD vaccines, immune complex and recombinant vaccines namely viral vector vaccine using serotype 3 of Marek's disease virus (MDV), the herpesvirus of turkey (HVT) have been used to control IBD in commercial poultry flocks (Alkie & Rautenschlein, 2016). The HVT-based IBD vaccines induce protection against two or more of the different diseases depending on the vaccine constructs expressing the immunogenic proteins such as avian influenza virus (Li et al., 2011), NDV (Reddy et al., 1996), and IBDV (Tsukamoto et al., 2002). Presently, the HVT-based IBD vaccine technology can provide protection against MDV as well as, other diseases such as avian influenza virus, Newcastle disease, and IBD where the vaccine constructs expressed the hemagglutination (HA) gene, fusion (F) gene, and VP2 gene, respectively (Li et al., 2011, Reddy et al., 1996, (Tsukamoto et al., 2002, Criado et al., 2023).

Recently, a new generation HVT-based IBD vaccine, that expressed the classical VP2 of IBDV, Faragher 52/70 strain, and the F gene of genotype VII NDV has been developed (Boehringer Ingelheim, 2024). The efficacy of this new generation HVT vaccine has not been fully evaluated in commercial chickens.

1.2 Research Problems

Infectious bursal disease virus causes significant immunosuppression effects to the chicken, the main approach to control the disease is vaccination. However, still, vaccination programs are affected by different issues, with the emergence of antigenic variants due to genetic mutations, recombination, and reassortments that may influence vaccine efficacy (Jackwood et al., 2011, Müller et al., 2012). Recently, a novel variant of IBDV has been detected in IBD-vaccinated poultry flocks in Malaysia. Although the virus was isolated from an apparently health flock, the performance of the birds was affected and the birds were showing secondary infection, proposing that IBD vaccination unable to provide complete protection against the variant IBDV (Aliyu et al., 2021; Wang, Jiang, et al., 2021; Yang et al., 2021).

It is crucial to investigate the pathogenicity and immunosuppression of the newly detected variant of IBDV in commercial broiler chicks. Additionally, it is important to determine the effectiveness of currently available commercial vaccines against this variant. Two different types of commercial HVT-based vaccines are being studied in this study, the HVT+IBD with the classical Faragher 52/70 and the newly developed HVT+IBD+ND containing classical

Faragher 52/70 and the F gene from genotype VII NDV. The HVT+IBD+ND is a new vaccine that expresses the F gene of genotype VII NDV, which makes this research even more important. Hence, the study aims to evaluate the immunogenicity and efficacy of commercial IBDV against the Malaysian variant IBDV and to assess the immunosuppressive effects of the variant IBDV in commercial broiler chickens. This study will provide valuable information on effective control and prevention strategies against variant IBD in commercial poultry flocks.

1.3 Research Hypothesis

Vaccination with two commercial HVT+IBD and HVT+IBD+ND vaccines in commercial broiler chickens induces comparably similar antibody titers against IBD as detected by ELISA.

Vaccination with the commercial HVT+IBD and HVT+IBD+ND vaccines in commercial broiler chickens induce comparable similar antibody titer against IBD and mild bursal lesions, compared to live attenuated IBDV vaccine.

Infection with the Malaysian variant IBDV inhibits the production of antibody titer following ND vaccination in broiler chickens.

1.4 Research Objectives

1. To determine the antibody responses based on ELISA and bursal lesion score following vaccination with commercial HVT+IBD, HVT+IBD+ND, and IBD BLEN vaccines in broiler chickens.

2. To reactivate, propagate, and titrate the Malaysian variant (UPM1432-2019) IBDV as a challenge virus in SPF chickens.

3. To determine the efficacy of commercial HVT+IBD and HVT+IBD+ND vaccines in conferring protection against Malaysian variant (UPM1432-2019) IBDV infection in broiler chickens.

4. To evaluate the immune suppression of Malaysian variant IBDV on ND vaccination in broiler chickens.

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