UNIVERSITI PUTRA MALAYSIA

GENOME SEQUENCING AND PATHOGENICITY OF RECENT INFECTIOUS BURSAL DISEASE VIRUSES IN MALAYSIA

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FPV 2021 12

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By

ALIYU HAYATUDDEEN BAKO

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

April 2021

DEDICATION

To my beloved parent (Alh. Aliyu and Noor Rukayya).
May Allah shower His mercy upon them and make Jannatul Firdaus their final abode, ameen.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

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Chairperson : Professor Aini Ideris, PhD
Faculty : Veterinary Medicine

Infectious bursal disease virus (IBDV) is an immunosuppressive viral pathogen that causes infectious bursal disease (IBD) in susceptible young chickens worldwide. Vaccination is a critical component in controlling IBD. The IBDV has a high genetic mutation rate which may result in antigenic variant. Antigenic variants have been reported from several laboratories including countries in Asia. The last characterisation of Malaysian IBDV full genome was in the year 2008. However, there is paucity of information on the recent characterisation and pathogenicity of IBDV isolated from commercial flocks in Malaysia. The present study focused on the genome-wide analysis of recently isolated IBDV in Malaysia using NGS technology, and the pathogenicity of the characterised strains were evaluated in specific pathogen-free (SPF) and immunised SPF chickens. Thirty bursal samples were used for the study, where 25 samples were collected from tentatively IBD diagnosed flocks in a commercial vaccinated broiler farm, and 5 samples were earlier submitted to the laboratory of vaccine and biomolecules, IBS. Eleven positive IBDV isolates were investigated. The isolates were detected using reverse transcription-polymerase chain reaction (RT-PCR) targeting the hypervariable region (HVR) of the VP2 gene. The nucleotide and amino acid (aa) sequences were compared with the previously characterised IBDV strains. Based on the VP2 sequences, five IBDV isolate were selected for whole-genome sequencing using the MiSeq platform. Pathogenicity of UPM1056/2018 (vvIBDV) and UPM1432/2019 (vaIBDV) strains was evaluated in 4-week-old (SPF) chickens. The chickens were randomly divided into 3 groups; group 1 (control), groups 2 and 3 birds were challenged with the vaIBDV and vvIBDV, respectively. Three birds from each group were weighed, euthanised and necropsied at 2, 3, 4, 5, 7 and 21 dpc. Pathological lesions were evaluated, and viral load in the tissues and cloacal shedding were determined. Immune-complex classical vaccine (vaccine A) and attenuated live very virulent vaccine (vaccine B) were used for immune-protection experiments in SPF chickens. One-day-old (n=75) SPF chickens were randomly divided into 3 groups of 25 chicks each. Group 1 (control), group 2 (Vaccine A) and group 3 (Vaccine B). Variant IBDV, UPM1432/2019 was used for the challenge at 21- and 28- days post vaccinations (dpv). Five birds from unchallenged and challenged groups were sacrificed at 7 dpc, and blood, bursa, spleen,

and cloacal swabs were collected. Antibodies (Ab), lymphoid lesions and viral load were determined. Deduced aa sequences of HVR revealed the characteristic motifs that showed seven isolates belong to very virulent strains (genogroup 3), two isolates belong to variant strains (genogroup 2), and two have an identity to vaccine strain (genogroup 1) of IBD viruses. The serine rich-heptapeptide sequence "SWSASGS" was conserved in all 11 isolates. Also, the complete genome sequences revealed the presence of aa substitutions; 12 in VP5, 15 in VP2, 5 in VP4, 4 in VP3 and 10 in VP1 for vaIBDV, UPM1432/2019 strain. UPM1056/2018 strain showed highest aa substitutions among the vvIBDV strains with aa substitutions; 2 in VP5, 8 in VP2, 4 in VP4, 5 in VP3 and 2 in VP1. Unlike the other vvIBDV characterised in this study, UPM766/2018 lacks the MLSL aa residues in VP5, whilst IBS536/2017 has 154 aa. The aa tripeptides: 145/146/147 (TDN) of VP1 were conserved for the vvIBDV, while NED was observed for the variant IBDV. The phylogenetic analysis showed that the isolates formed clustered with the respective genogroups. The vaIBDV clustered with the American and Chinese variant viruses and highly comparable to the Chinese novel variants with 99.9 % identity. While the vvIBDV grouped with the vvIBDV of other countries, but they are closely related to the previously characterised Malaysian vvIBDV. Unlike UPM1056/2018 group, birds from UPM1432/2019 group did not show clinical signs or death. Both strains induced pathological lesions on the BF in the infected chickens with a more severe lesion in UPM1056/2018 group. The bursal body index (BBIX) for UPM1432/2019- and UPM1056/2018 groups was < 0.7 from 2 dpc and continued to decrease to 0.49 and 0.45, respectively at 21 dpc. UPM1432/2019 strain was detected for longer duration in the bursa than UPM1056/2018 strain. The variant strain, UPM1432/2019, induced bursal damage in immunised chickens in the presence of antibodies titres at two different age groups, 28- and 35- dpv (7 dpc). The BBW of vaccinated unchallenged groups did not differ significantly ($P > 0.05$) from that of the vaccinated challenged groups. But the mean BBW for the unchallenged control group was higher ($P < 0.0001$) than for the control challenged group. Microscopically, the bursae of the challenged groups showed significant atrophy, particularly in the control group. The bursal lesion score was higher ($P > 0.05$) in control and vaccine B challenged groups than that in vaccine A challenged group of the two-challenge periods. Also, the viral loads were significantly higher ($P < 0.01$) in the bursa than in the spleen, and the highest ($P < 0.05$) viral load was found in control challenged group than the vaccinated ones. The study has reported IBDV variant for the first time in Malaysia, and the majority of IBDV circulating in Malaysia are evolving very virulent strain. Both the vaIBDV and vvIBDV induced similar pathological lesions in SPF chicks. The two vaccines could not adequately protect against the Malaysian vaIBDV challenge. Our findings explained the urgent need for the development of new vaccines against the vaIBDV. Further research is required to assess the potentiality of vaccine development from the variant strain.

Abstrak yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan ijazah untuk Doktor Falsafah

PENJUJUKAN GENOM DAN PATOGENISITI VIRUS PENYAKIT BURSA BERJANGKIT BARU DI MALAYSIA

Oleh

ALIYU HAYATUDDEEN BAKO

April 2021

Pengerusi : Profesor Aini Ideris, PhD
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Virus penyakit bursa berjangkit (IBDV) adalah patogen virus imunosupresif yang menyebabkan penyakit bursa berjangkit (IBD) pada ayam muda yang mudah dijangkiti di seluruh dunia. Vaksinasi adalah komponen kritikal untuk mengawal IBD. IBDV mempunyai kadar mutasi genetik yang tinggi yang boleh menyebabkan varian antigenik.Varian-varian antigenik telah dilaporkan di beberapa makmal termasuklah negara-negara di Asia. Pencirian penuh genom IBDV Malaysia yang terakhir direkodkan pada tahun 2008. Walaubagaimanapun, terdapat kekurangan maklumat mengenai ciri-ciri dan patogenisiti IBDV yang diasingkan daripada kumpulan ladang ayam pedaging komersial di Malaysia, yang diberi vaksin. Kajian ini memfokuskan analisis *genome-wide* dengan menggunakan teknologi NGS terhadap isolat baru IBDV Malaysia. Kebolehjangkitan strain kemudian telah dievaluasi di dalam ayam *specific pathegen free* (SPF) dan ayam SPF yang telah diimunisasi. 30 sampel bursa telah digunakan dalam kajian ini, di mana 25 sampel dikumpulkan daripada ayam yang telah dijangkiti IBD di ladang ayam komersial yang telah divaksinasi, dan daripada lima sampel yang telah dihantar ke makmal vaksin dan biomolekul, IBS. Jujukan asid amino (aa) telah dibandingkan dengan strain isolat yang telah dicirikan terlebih dahulu. Berdasarkan jujukan VP2, lima isolat IBDV telah dipilih untuk proses jujukan lengkap genom dengan menggunakan platform MiSeq. Patogenisiti strain UPM1056/2018 (vvIBDV) dan UPM1432/2019 (vaIBDV) telah dievaluasi di dalam ayam SPF yang berumur 4-minggu. Ayam-ayam tersebut telah dibahagikan kepada 3 kumpulan secara rawak; kumpulan 1 (kontrol), kumpulan 2 dan 3 masing-masing telah dicabar dengan vaIBDV dan vvIBDV. Tiga ekor ayam dari setiap kumpulan telah ditimbang, dikorban dan dinekropsi pada hari ke-2, 3, 4, 5, 7 dan 21 pasca-cabaran (dpc). Lesi patologi telah dinilai dan beban virus dalam tisu-tisu dan *cloacal shedding* telah ditentukan. Vaksin klasik *immune-complex* (vaksin A) dan vaksin hidup sangat virulen yang dilemahkan (vaksin B) telah digunakan untuk eksperimen perlindungan imun di dalam ayam SPF. Ayam SPF yang berumur satu hari (n=75) telah dibahagikan secara rawak kepada tiga kumpulan yang mengandungi 25 ekor anak ayam untuk setiap kumpulan. Kumpulan 1 (kawalan), 2 (Vaksin A) dan 3 (Vaksin B). Varian IBDV, UPM1432/2019 digunakan untuk cabaran pada hari ke-21 dan ke-28 pasca vaksinasi (dpv). Lima ekor ayam masing-masing dari

kumpulan yang tidak dicabar dan kumpulan yang dicabar telah dikorbankan pada 7 dpc, dan darah, bursa, limpa dan *cloacal swabs* telah dikumpulkan. Titer antibodi (Ab), lesi limfoid dan beban virus telah ditentukan. Jujukan aa pada rantau HVR yang diperolehi mendedahkan ciri-ciri motif yang menunjukkan tujuh isolat tergolong dalam strain sangat virulen (*genogroup 3*), dua isolat tergolong dalam strain varian (*genogroup 2*) dan dua isolat mempunyai identiti strain vaksin (*genogroup* 1) virus-virus IBD. Jujukan *serine rich-heptapeptide* (SWSASGS) telah dipelihara dalam kesemua 11 isolat. Juga, jujukan genom lengkap mendedahkan kehadiran penggantian aa; 12 dalam VP5, 15 dalam VP2, 5 dalam VP4, 4 dalam VP3 dan 10 di dalam VP1 untuk strain vaIBDV, UPM1432/2019. Strain UPM1056/2018 menunjukkan penggantian aa tertinggi di kalangan strain-strain vvIBDV dengan penggantian aa; 2 dalam VP5, 8 dalam VP2, 4 dalam VP4, 5 dalam VP3 dan 2 dalam VP1. Tidak seperti vvIBDV lain yang dicirikan dalam kajian ini, UPM766/2018 tidak mempunyai residu aa MLSL dalam VP5, manakala IBS536/2017 mempunyai 154 aa. Tripeptida aa; 145/146/147 (TDN) VP1 telah dipelihara untuk vvIBDV, manakala motif NED didapati untuk varian IBDV. Analisis filogenetik menunjukkan isolat membentuk kluster bersama *genogroup* masing-masing. Varian IBDV membentuk kluster bersama virus varian Amerika dan Cina dan sangat setanding dengan varian baru Cina dengan identiti 99.9%. Walaupun vvIBDV dikumpulkan dengan vvIBDV dari negara-negara lain, mereka juga berkait rapat dengan vvIBDV Malaysia yang telah dicirikan sebelumnya. Tidak seperti kumpulan UPM1056/2018, burung-burung daripada kumpulan UPM1432/2019 tidak menunjukkan tanda-tanda klinikal atau kematian. Kedua-dua strain meransang lesi patologi pada BF di dalam ayam yang telah dijangkiti dengan lesi yang lebih parah pada kumpulan UPM1056/2018. Indeks badan bursa (BBIX) bagi kumpulan UPM1432/2019 dan UPM1056/2018 masing-masing adalah < 0.7 daripada 2 dpc dan terus berkurangan kepada 0.49 dan 0.45, masing-masing pada 21 dpc. Strain varian UPM1432/2019 mendorong kerosakan bursa di dalam ayam yang telah diimunisasi dengan kehadiran titer antibodi pada dua kumpulan umur berbeza, 28- dan 35-dpv (7 dpc). BBW untuk kumpulan yang diberi vaksin dan tanpa dicabar tidak menunjukkan perbezaan ketara ($P > 0.05$) daripada kumpulan yang diberi vaksin dan dicabar. Tetapi, purata BBW untuk kumpulan kawalan yang tidak dicabar adalah lebih tinggi ($P < 0.0001$) berbanding kumpulan kawalan yang dicabar. Secara mikroskopik, bursa kumpulan yang dicabar menunjukkan atrofi yang ketara, terutamanya di dalam kumpulan kawalan. Skor lesi bursa adalah ketara lebih tinggi ($P > 0.05$) di dalam kumpulan kawalan dan kumpulan vaksin B yang dicabar berbanding kumpulan vaksin A yang dicabar pada tempoh dua-cabaran. Juga, beban virus ketara lebih tinggi ($P < 0.01$) di dalam bursa berbanding limpa, dan beban virus yang tertinggi ($P < 0.05$) ditemui di dalam kumpulan kawalan yang dicabar berbanding kumpulan yang diberi vaksin. Kajian ini melaporkan varian IBDV yang pertama di Malaysia, dan majoriti IBDV yang beredar di Malaysia adalah strain yang sangat virulen dan berkembang. Kedua-dua vaIBDV dan vvIBDV mendorong lesi patologi yang serupa di dalam anak ayam SPF. Kedua-dua vaksin tidak dapat melindungi sepenuhnya cabaran oleh vaIBDV Malaysia. Penemuan kami menjelaskan keperluan mendesak untuk pembangunan vaksin baru terhadap vaIBDV. Penyelidikan lanjut diperlukan untuk menilai potensi pembangunan vaksin dari strain varian.

ACKNOWLEDGEMENTS

Bismillahirrahmanirrahim.

All praises due to almighty ALLAH, Lord of the world, the beneficent, the gracious and the most merciful for His countless bounties upon me throughout life and my study journey. Also, May Allah honours His beloved prophet and grant him peace.

I would like to express my sincere gratitude and appreciation to my supervisor, Prof. Datin Paduka Setia Dato Dr Aini Ideris, who granted me an exceptional opportunity to work under her watch. I am overwhelmed by her excellent research ideas, patience, and thorough guidance, which piloted my research into success. The thesis would not be completed without her superb support. To my supervisory committee members, Prof. Dr Abdul Rahman Omar, and Prof. Dato Dr Mohd Hair-Bejo for supervising all stages of the research work and their constructive criticisms, patience, support and guidance, which made my PhD journey a reality.

The role of the Tertiary Education Trust Fund (TETFund) under the Ministry of Education, Nigeria, is enormous. It cannot be overemphasised, being the backbone of the financial support for this research journey. Also, the same goes to my employer, Ahmadu Bello University (ABU), Zaria, who nominated me for this outstanding achievement without which my PhD journey would have been a different story.

A special thanks go to Dr Tan Sheau Wei, of Laboratory of Vaccine and Biomolecules, Institute of Bioscience for her endurance and guidance during my laboratory work. I acknowledge the support given to me by my postgraduate colleagues; Dr Bashir, Dr Iswadi, Raji, Tasi'u, Salisu, Syazana, Rohaya, Azizah, Sue and those whose names were not mentioned who contributed in any kind to the success of this PhD journey. Words would not express my appreciation to all.

This research work could not have been completed without the assistance of the staff of Laboratory of Vaccine and Biomolecules; Puan Norhafiza, Puan Nadia, Puan Norhaszalina, and Puan Nancy as well as En. Saipuzaman Ali in Serology Laboratory. To all the staff and lecturers in all Departments of the Faculty of Veterinary Medicine, Universiti Putra Malaysia, particularly Prof. Goh Yong Meng for their contribution to the successful completion of my PhD.

I am pleased to use this opportunity to pay tribute to the School of Graduate Studies, Universiti Putra Malaysia for continuous education through seminars and workshops, which tremendously added juice to the PhD journey. My heartfelt gratitude goes to the Universiti Putra Malaysia for providing me with the enabling environment for this research work.

To my parents, indeed they will never be forgotten for everything they impacted on me, which make me proud today. I ask the Lord Almighty to reward them, forgive their

shortcomings and grant them Jannah. I would like to express my deepest gratitude to my lovely wife and children for their unconditional love and encouragement. Without their support and patience, I could not have made it thus far. To my family, I sincerely appreciate their care and prayers.

My special thanks go to my mentor Prof. Lawal Sa'idu, for his continuous support and advice in this research journey. The same appreciation goes to Prof. Paul Ayuba Abdu. I would like to pay tribute to all my teachers and co-workers in the Avian Unit, Veterinary Teaching Hospital, ABU, Zaria. To my friend Abubakar Abubakar Ahmad, I sincerely appreciate his kindness during my stay in Malaysia. Thank you, and I love you all.

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirements for the degree of Doctor of Philosophy. The members of the supervisory committee were as follows:

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Date: 9 December 2021

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aa	Amino acid
AC-ELISA	Antigen Capture-Enzyme-linked immunosorbent assay
AGP	Agar gel precipitation
ANOVA	Analysis of variance
AP-1	Activating protein-1
APC	Antigen presenting cell
B	Base
BBIX	Bursal body index
BBW	Bursal to body weight ratio
BF	Bursa of Fabricius
BGM-70	Buffalo green monkey kidney
BLAST	Basic local alignment search tools
BLS	Bursal lesion score
BLT	Bead-linked transposome
bp	Base pair
CAM	Chorioallantoic membrane
CARD	Caspase activation and recruitment domain;
Casp	Caspase
CD	Cluster of differentiation
cDNA	Complementary deoxyribonucleic acid
CEE	Chicken embryonated eggs
CEF	Chicken embryo fibroblast
ChIL	Chicken interleukin
CMI	Cell-mediated immunity

Cq	Quantification cycle
CTL	Cytotoxic T cell
cvIBDV	Classical virulent infectious bursal disease virus
CXCLi	Chemokine (C-X-C motif) ligand
Cyto-C	Cytochrome c
dIBDV	Distinct infectious bursal disease virus
DIVA	Differentiation of infected versus vaccinated animals
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
dNTP	Deoxyribonuclotide triphosphate
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
Eif	Eukaryotic initiation factor
ELISA	Enzyme-linked immunosorbent assay
EPM	Enhanced PCR mix
FAM	6-carboxyflouricein
GILZ	Glucocorticoid-induced leucine zipper
Gzm-A	Granzyme-A
HMG	High mobility group protein
HSP90α	Heat shock protein 90 alpha

HVR	Hypervariable region
HVT	Herpesvirus of turkey
IBD	Infectious bursal disease
IBDV	Infectious bursal disease virus
Icx	Immune complex
IDA	Isoleucine-Aspartate-Alanine
IFN	Interferon
Ig	Immunoglobulin
IgM	Immunoglobulin M
IL	Interleukin
iNOS	Inducible nitric oxide synthetase
IRF	Interferon regulatory factor
JNK	C-Jun-N-terminal kinase
LAMP	Loop mediated isothermal amplification
Mab	Monoclonal antibody
MAVS	Mitochondrial antiviral signalling protein
MDA	Maternally derived antibody
MDA5	Melanoma differentiation-associated gene 5
MHC	Major histocompatibility complex
MIP	Macrophage inflammatory protein
mL	Millilitre
mM	Milli Molar
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
nM	Nanomolar
NO	Nitric oxide
nts	nucleotides
^{o}C	Degree Celsius
OIE	Office
ORAOV1	Oral cancer overexpressed 1
ORF	Open reading frame
P	Projection
PARP	Poly (ADP-ribose) polymerase
PBS	Phosphate buffer saline
PFN	Perforin
PI3K	Phosphoinositol-3 kinase
PP	Polyprotein
PTC	Post tagmentation clean up
R^2	Coefficient of correlation
RACK1	Receptor of activated protein kinase C1
RdRp	RNA dependent RNA polymerase
RE	Restriction enzyme
RFLP	Restriction fragment length polymorphism
RNA	Ribonucleic acid
ROS	Reactive oxygen species
Rpm	Revolution per minute

RT	Reverse-transcription
RT-PCR	Reverse-transcription polymerase chain reaction
RT-qPCR	Quantitative reverse-transcription polymerase chain reaction
S	Shell
SBW	Spleen to body weight ratio
SPB	Sample purification beads
SPF	Specific pathogen free
SVP	Subviral particle
TAE	Tris-acetate-EDTA
TAG	Tagmentation
Th1	T helper cell 1
Th2	T helper cell 2
TLR	Toll-like receptor
Tm	Melting temperature
TNF	Tumour necrosis factor
Treg	T regulatory
tRNA	Transfer ribonucleic acid
TSB	Tagment stop buffer
TWB	Tagment wash buffer
UK	United Kingdom
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 neutralisation
VP	Viral protein
VRI	Veterinary Research Institute
vRNA	Viral RNA
vvIBDV	Very virulent infectious bursal disease virus
w/v	Weight per volume
%	Per cent
µg	Micogram
µL	Microlitre
α	Alpha
β	Beta
γ	Gamma

CHAPTER 1

INTRODUCTION

1.1 Background of the Study

Poultry production is an important sector in the livestock industry all over the world. In the first quarter of the year 2021, the world poultry production was reported to be about 102.1 million tons (USDA, 2021). The goal of the industry is to provide enough quality meat and eggs to the growing population. Malaysia has shown a steady increase in poultry production, particularly broiler sector in recent years (Bahri et al., 2019). However, the industry is facing some obstacles that slow down production efficiency. One of the militating problems of broiler meat for Malaysian citizen is that IBD caused serious impact to the broiler meat. This impact contributes to the increased production cost. The essential factors that contribute to the increased production cost apart from the feed (Shaban & Alabboodi, 2019) are disease management. One of the acute viral diseases that militates against the poultry farming in Malaysia is the infectious bursal disease (IBD) outbreaks. This condition exposes the affected birds to other pathogens and results in poor feed conversion ratio; thus, it increases the production cost.

The IBD is a significant disease of young chickens that continues to be a main setback for the fast-growing poultry industry throughout the world. It is an extremely infectious viral disease of poultry, causing considerable economic losses due to immunosuppression and high mortality (up to 90%) in susceptible chickens (Lim et al., 1999; Aliyu et al., 2016). The aetiological agent is infectious bursal disease virus (IBDV), which is a single-shelled, non-enveloped, double-stranded (ds) RNA virus belonging to the family Birnaviridae of the genus Avibirnavirus (Azad et al., 1985).

The virus is highly stable, and being that it resists many disinfectants (Enterradossi & Saif, 2013; Aliyu et al., 2016). The virus has been reported to persist and be infectious for 122 days in a poultry house and 52 days in feed and water (Müller et al., 2012). The virus has an affinity for immature B lymphocytes in the bursa of Fabricius (BF), which is a primary lymphoid structure of birds, and thereby resulting in B-cell depletion (Muller et al., 1979). Its genome consists of two segments, A and B of 6 kb total length (Müller et al., 1979). Segment A (~3.3 kb) contains two partly overlapping open reading frames (ORFs) that encode for non-structural protein (VP5, 17kDa) and precursor polyprotein (VP2-VP4-VP3, 110kDa). The polyprotein is autoproteolytically cleaved to yield capsid proteins (VP2 and VP3) and a serine protease (VP4). The segment B (~2.9 kb) encodes VP1 (97 kDa), which is RNA-dependent RNA polymerase responsible for viral replication (Macreadie & Azad, 1993). Viral capsid protein (VP2) and ribonucleoprotein (VP3) are the main structural proteins, accounting for 51% and 40% of the virion, respectively (Dobos et al., 1979).

The virus was initially discovered in 1957 in the U.S. as a mild pathogen that caused slight clinical signs in susceptible chickens. At that time, the disease did not create a significant impact on the poultry industry due to effective control of classical IBDV strain by vaccination. Also, the condition was limited to some geographical regions. Several vaccines have been developed, and more are under trial to target vvIBDV strains that came to existence in the late 1980s and more importantly, the current evolving antigenic variants (Mundt et al., 2003). Vectored and immune complex (Icx) vaccines have been developed and licensed to solve the ineffectiveness associated with the classical vaccines (Rautenschlein & Alkie, 2016). The Icx vaccine is delivered in 1-day-old at the hatchery through subcutaneous route (Iván et al., 2005), and the vaccines have been proven efficient even in the presence of maternally derived antibodies (MDA) (Giambrone et al., 2001). Also, previous experimental challenge studies demonstrated that Icx vaccine presented better protection than live conventional IBDV vaccines (Müller et al., 2012). Besides, more genetically engineered vaccines are developed to checkmate the antigenic variation that is fast evolving within the viruses. Yet, emerging strains of IBDV are taking different dimension which continues to cause economic impact to the poultry industry worldwide.

Furthermore, the circulating strains are only identifiable by surveillance and molecular characterisation of the field isolates. Among the high-throughput molecular profiling in the advancement of diagnostic virology are microarray and NGS technologies. These recent technologies are employed for in-depth molecular analysis of intending viruses. Next-generation sequencing (NGS) is one of the recent advances in diagnostic molecular virology replacing Sanger's sequencing method in various sequencing projects. The robustness, low cost, and accuracy of NGS has made it possible to analyse the genetic diversity of avian pathogens e.g., Adenovirus, Herpesvirus, Avibirnavirus etc. Pre-amplification using RT-PCR provides fewer viruses, and more overlapping sequences detected with lower coverage (Li et al., 2015). Amplicon-based NGS is limited in detecting pre-defined targets; thus, it is crucial to have an efficient viral nucleic acid extraction for high sensitivity and reliability of NGS output (Klenner et al., 2017).

1.2 Research Problems

The IBDV causes irreversible immunosuppression in young chickens, which render them more susceptible to many opportunistic avian pathogens (Saif, 1991). The disease is controlled using efficacious vaccines. Still, vaccination efforts are confronted with challenges of frequent genetic mutations, reassortments and recombination that may enhance virulence and modify antigenicity, rendering vaccines and vaccine practices ineffective (Jackwood et al., 2008; Qi et al., 2009; Jackwood & Sommer-Wagner, 2011; He et al., 2016).

Following the first report of IBDV in 1957 in the USA (Cosgrove, 1962), IBD was satisfactorily controlled using classical IBD virus vaccine. But with the emergence of vvIBDV in the late 1980s, control of IBD has become a challenge. However, the continuous evolution of this virus poses an alarm to the then growing poultry farming, and pieces of research have been carried out to put a halt to the impact of the circulating strains. Several vaccines have been developed to target the existing vvIBDV strains.

Being an immunosuppressive, the response of chickens to the disease outbreaks in vaccinated flocks has been through the use of intermediate plus (hot) vaccines (Mahgoub, 2012). It is, therefore, trying for the host to neutralise the infectious disease in which the causative agent precisely invades the defence system (Qin & Zheng, 2017). A previous study has demonstrated a growing concern that IBDV may continue to increase virulence due to potential mutation through the use of intensive live attenuated vaccines against IBD (Mahgoub, 2012).

However, the current antigenic drift of the virus has made it difficult to control the virulent outbreaks around the world. Antigenic drift among the IBDV serve as a significant limitation to the universal application of vaccines against IBD, in that new antigenic strains of the virus is limited to specific geographical area (Jackwood & Stoute, 2013). Besides, being it the most critical viral gene, VP2 mutation indicates that specific codons are under continuous selection pressure and antigenic drift, which possibly favour evolving neutralising antibody (Ab) escape mutants (Vukea et al., 2014). These escape mutants were as a result of a mutation at the major hydrophilic peaks A and B of VP2 HVR (Umm-I-Habiba et al., 2020).

Nevertheless, based on previous works on reverse genetics, some domains of the IBDV polymerase might contribute to the virulence of the virus (Pan et al., 2007; Le Nouen et al., 2012). Gao et al. (2018) suggested that the N-terminal domain of IBDV VP1 is more crucial in the pathogenicity of vvIBDV to the central polymerase and the C-terminal domains. Although VP2 protein was considered to be the essential gene in tissue tropism and pathogenicity (Brandt et al., 2001), it was, however, proved not to be the only factor for the virulence of vvIBDV. Therefore, the pathogenicity of vvIBDV is dependent mainly on the mechanisms involving proteins from both segments, A and B (Escaffre et al., 2013). Moreover, spontaneous genetic reassortment and homologous recombination contribute to the evolution of IBDV (He et al., 2009). Consequently, more IBDV antigenic variations are evolving across the global poultry producing regions resulting in reassortants (Hussain et al., 2020) and recombinants (Jackwood, 2012; Wu et al., 2020) strains.

Furthermore, identification and characterisation of new emerging IBDV strains remain a principal focus for the development of new vaccination approaches (Rautenschlein & Alkie, 2016). More detailed understanding of emerging IBDV pathogenesis and host-pathogen interaction concerning the immune organs is necessary to provide improved control measures (Ingrao et al., 2013). Hence, NGS technologies and bioinformatics are significant for the understanding of IBDV epidemiology, and the analyses predict the spread of some strains in the field (Rautenschlein & Alkie, 2016) as well as the factors responsible for spontaneous genome assortment (Kasanga et al., 2013). Monitoring the evolution of antigenic variants remains the best approach to reduce the mismatch between vaccine strains and wild-type viruses.

In Malaysia, the first IBD case was reported in 1991 (Hair-Bejo, 1992), and since then, vvIBDV strains are being reported (Phong et al., 2003; Kong et al., 2004; Nurulfiza et al., 2006). No report of antigenic variant for the characterised IBDV in Malaysia, but several variants, reassortants and recombinant strains have been reported in Asia,

especially China. Hence the need for continuous characterisation of the circulating IBDV strains so that, vaccines and vaccination programmes be adopted for the current epidemiological situation. Besides, most of the molecular characterisation of IBDV isolates was mainly on the partial sequencing of VP2 gene (Phong et al., 2003; Tan et al., 2004). However, genome sequencing and pathogenicity of IBD viruses are limited in Malaysia. Therefore, this study focuses on the genome-wide analysis of recent IBDV isolated in Malaysia using NGS technology, and the pathogenicity of the characterised strains are evaluated in SPF and immunised SPF chickens.

Research Hypothesis

1. The IBD viruses may undergo mutations especially in the VP2 hypervariable region.

2. Next-Generation Sequencing can generate a draft genome of IBDV.

3. Emerging strains of Malaysian IBDV have diverse genetic profiles.

4. The current available IBD vaccines can confer full protection in chickens against circulating Malaysian IBDV strains.

Research Objectives

General objective

The study focused on the genome-wide analysis of recent Malaysian IBDV and the pathogenicity of the characterised strains in SPF and immunised SPF chickens.
The specific objectives of this study were:

1. To detect Malaysian IBDV isolates (2017 to 2019).

2. To sequence whole genome of recent Malaysian IBDV isolates.

3. To determine the genome characteristics of the recently characterised Malaysian very virulent and variant IBDV strains.

4. To determine the pathogenicity of the recently characterised Malaysian very virulent and variant IBDV in SPF chickens.

5. To determine the immune-protective efficiency of some commercially available IBD vaccines against Malaysian variant IBDV in SPF chickens.

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