P-ISSN: 2304-3075; E-ISSN: 2305-4360
International Journal of Veterinary Science
www.ijvets.com; editor@ijvets.com

Research Article https://doi.org/10.47278/journal.ijvs/2025.037

Efficacy, Safety and Virus Shedding of Inactivated Very Virulent Infectious Bursal Disease Virus in Broiler Chickens

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Article History: 24-769 Received: 31-Dec-24 Revised: 10-Feb-25 Accepted: 17-Feb-25 Online First: 11-Apr-25

ABSTRACT

The development of vaccines against very virulent infectious bursal disease virus (vvIBDV) has become pertinent due to the inability of current IBD vaccines to provide full protection. This study aimed to inactivate and evaluate the efficacy and safety of inactivated vvIBDV in broiler chickens. An aliquot of the virus was inactivated by the Binary Ethylene Inime (BEI) method, checked for sterility, and stored at 4˚C. Sixty-day-old commercial broiler chickens were grouped into A (non-booster), B (booster), and C (control). Groups A and B were inoculated with 10^7 EID_{50}/0.2mL inactivated vvIBDV subcutaneously at day old. Group B received a booster dose on experimental day 14 while Group C was uninoculated. On day 28, challenged Groups A, B, and C were separated from Groups A, B, and C respectively, and challenged with a pathogenic vvIBDV field strain of 10^5 EID_{50}/1.0mL via eye drops (0.2mL) and orally (0.8mL). No clinical manifestation was observed in all groups. Chickens in the booster group showed increased body and bursa weight; bursa: and body weight ratio post-challenge. The bursa of Fabricius for all the non-challenged groups appeared normal grossly and histologically. The challenged control group (CCH) showed moderate-severe to severe bursa lesions, indicating a positive vvIBDV infection. Bursal lesion scoring of the challenged booster group was significantly lower ($P<0.05$) than the other groups. The control-challenged group recorded the highest antibody titer while the booster group had the least, indicating protection. The booster group also had the least viral shedding among all challenged groups. These findings suggested that the inactivated vvIBDV vaccine candidate was safe and efficacious in chickens and could be a good vaccine candidate against vvIBDV in chickens especially when boosted after 14 days.

Key words: Infectious bursal disease, vvIBDV, Inactivated vaccine, Efficacy, Safety, Virus shedding.

INTRODUCTION

Infectious bursal disease (IBD), or the Gumboro disease is a highly contagious and immunosuppressive disease in 3-6 weeks old chickens leading to heavy economic losses in the poultry industry worldwide (Myint et al. 2020; Huang et al. 2023; Hayajneh and Araj 2023). It is caused by IBD virus (IBDV) which is a double-stranded RNA virus belonging to the genius, Avibirnavirus in the family Birnaviridae (Dey et al. 2019). The virus is categorized into three, classical (ca), variant (va), and very virulent (vv) IBDV (Khan 2018). The vv strain is responsible for acute morbidity and mortality in young chickens with destruction of the lymphoid organs, especially the bursa of Fabricius which is the site of maturation and differentiation of B lymphocytes (Cheng et al. 2023). Thus, birds infected with vvIBDV will also become immunosuppressed (Hair-Bejo et al. 2004; Trapp and Rautenschlein 2022).

A majority of conventional live IBDV vaccines available on the market are based on caIBDV and have limited efficacy against vvIBDV, especially with interference from high levels of maternally derived antibodies which have been reported to inhibit vaccine efficacy (Otero et al. 2020). Although “intermediate” or “intermediate-plus” vaccines possess better efficacy and can break through higher levels of maternally derived antibodies (MDA), they often cause moderate to severe bursal lesions which leads to immunosuppression of the flocks (Rautenschlein et al. 2005; Wang et al. 2022; Li et al. 2023; Zhang et al. 2024). Furthermore, they may not fully protect chickens against infection by vvIBDV strains

Cite This Article as: Mohd HB, Mazlan M, Ning CZ, Sohaimi NM and Clifford UC, 2025. Efficacy, safety and virus shedding of inactivated very virulent infectious bursal disease virus in broiler chickens. International Journal of Veterinary Science x(x): xxxx. https://doi.org/10.47278/journal.ijvs/2025.037

or antigenic vaIBDV. The safety and efficacy of this type of vaccine is a major concern.

Contrarily, the inactivated IBD vaccines are relatively safer and should be incorporated into the vaccination regime as an alternative to live vaccines. The ability of the inactivated IBD vaccines to induce IBDV-specific T-cells and inflammatory responses in chickens has been observed (Rautenschlein et al. 2002). Inactivated FAdV vaccines were also reported to induce T cells which protected experimentally infected chickens from pathogenic FAdV serotype 8b (Ugwu et al. 2022). Although killed vaccines are not ideal for inducing primary antibody response alone, its incorporation with oil in water adjuvant like Montanide 71VG stimulated longer-lasting immunity in chickens (Ugwu et al. 2022). Therefore, developing an inactivated vvIBDV vaccine with Montanide 71VG could aid in the prevention and control of vvIBDV infections.

This study was therefore carried out to determine the efficacy and safety of an inactivated vvIBDV with Montanide 71VG adjuvant inoculated into broiler chickens either as a single or double (booster) inoculation and challenged with a pathogenic field isolate of vvIBDV.

MATERIALS AND METHODS

Virus

The vvIBDV isolate, UPM0081 (B0081) with assession number AY520910, used in this study was obtained from a severe field outbreak of infectious bursal disease in Malaysia in 2000. It was passaged once in specific pathogen-free (SPF) chicken embryonated eggs (CEE), filtered through a 0.45µm syringe filter and stored as CAM homogenate in the Virology Laboratory, Faculty of Veterinary Medicine, Universiti Putra Malaysia. The isolate was used for inactivation and as a challenge virus for this experiment.

Ethics approval for the utilization of experimental animals

The Institutional Animal Care and Use Committee (IACUC) of University Putra Malaysia (UPM) approved the utilization of chickens for this experiment with reference number UPM/IACUC/ AUP-U014/2022 and their guidelines on handling animals were followed in this study.

Inactivation of vvIBDV Isolate UPM0081

Six mL of vvIBDV isolate was measured into a centrifuge tube and mixed with 120 µL of Binary Ethylene Inime (BEI) as an inactivating agent. The mixture was incubated at 37ºC for 36 hours. At every 30-minute interval, the mixture was mixed thoroughly with a vortex mixer. After 36 hours, 12µL of sodium thiosulfate was added to halt the action of the inactivating agent and mixed thoroughly with a vortex mixer at 37ºC for one hour. The inactivated vvIBDV isolate was then filtered through a 0.45µm syringe filter and confirmed inactivated by inoculation into SPF embryonated chicken eggs 2x without mortality. The inactivated isolate was mixed with Montanide 71 VG adjuvant, at the ratio of 30:70 (inactivated vvIBDV: Montanide 71 VG) and mixed thoroughly with a vortex mixer for 2 hours. The inoculum was stored at 4ºC until use.

Experimental design for the inactivated vvIBDV chicken trial

Sixty, day-old commercial broiler chickens were divided into six groups: A, ACH, B, BCH, C and CCH. They were housed in cages with controlled lighting and temperature and provided with feed and water *ad libitum*. At day-old (D0), Groups A, ACH, B, and BCH were inoculated subcutaneously (SQ) with 0.2mL of 10^7 EID_{50}/0.2mL inactivated vvIBDV and Groups C and CCH were uninoculated. Five birds from Group C (control) were sacrificed for the data collection on 0-day post inoculation (dpi) or 1 day of age and from each group on each sampling day (Table 1). On day 14 (D14), the same volume of inactivated vvIBDV was given to Groups B and BCH as a booster, while 5 birds from both Groups A and C were sacrificed for data collection. On day 28 (D28), the birds in Groups ACH, BCH, and CCH were challenged with 10^5 EID_{50}/1.0mL pathogenic field strain of vvIBDV via eye drops (0.2mL) and oral (0.8mL) routes. The birds were monitored for seven days post-challenge and were sacrificed for data collection. Clinical signs, gross lesions, body weight, and bursa weight were recorded while bursa to body weight ratio was calculated. Blood samples for antibody titer, bursa samples for histopathological changes, lesion scoring and viral load and cloacal swabs for virus shedding were collected.

Table 1: Design for the experimental animal trial of inactivated vvIBDV in commercial broiler chickens

Groups	Time (Days post inoculation (dpi))				
	0+	14*	28#	35	Total
A		5	5	5	15
ACH				5	5
B			5	5	10
BCH				5	5
C	5	5	5	5	20
CCH				5	5
Total					60

All chickens in A, ACH, B, and BCH groups were given inactivated vvIBDV at day old (+). Groups B and BCH received booster on 14 dpi (*) while groups ACH, BCH, and CCH received pathogenic vvIBDV on 28 dpi as a challenge. The numbers in the table represent the number of sampled chickens on each sampling day (#)

IBD antibody titer of chickens inoculated with inactivated vvIBDV and challenged

Serum was extracted from each blood sample collected from chickens at each sampling day within 24 hours after collection and stored at -20°C. Each serum was tested for IBD antibody titer using a commercial ELISA kit (BioChek, UK) following manufacturer's recommendation. Microtiter plate reader (Dynatech MR7000, USA) was used to record the absorbance at 405nm and the IBD antibody titer was generated using BioCheck 2000 software (Hair-Bejo et al. 2024).

Histopathology and lesion scoring

The samples of bursa of Fabricius from each chicken sampled previously fixed in 10% buffered formalin were processed with an automatic machine (Leica ASP 300) for 24 hours, and later embedded in heated paraffin wax and cooled to solidify, then trimmed and sectioned into 4µm. After that, fixation on glass slides and hematoxylin and

eosin staining was performed. Slides were examined for histological changes in bursa samples under a light microscope. Lesion scoring was graded based on a scale of 0 to 5; 0 (normal), 1 (mild), 2 (mild to moderate), 3 (moderate), 4 (moderate to severe), 5 (severe) (Hair-Bejo et al. 2000).

Viral loads and viral shedding

RNA extraction and purification from pooled samples of bursa and cloacal swabs from the challenged chickens in the 3 groups were done with a Kylt® RNA/DNA purification kit (SAN Group Biotech, Germany) following the manufacturer's recommendations. The purity of the extracted RNA was confirmed using a spectrophotometer (Eppendorf, Germany) at a 260 nm wavelength. RT-q PCR was carried out with specific nVarIBDV primers as previously described (Aliyu et al. 2021) and copy numbers were calculated.

Statistical Analysis

Data collected were analyzed using analysis of variance (ANOVA) on IBM SPSS Statistic 23 and mean separated on Turkey HSD post-hoc test. As the confidence interval of this study was 95%, the statistical results were only significant when $P<0.05$.

RESULTS

Clinical signs

No abnormal clinical signs were observed in the chickens in all the groups throughout the 35-day trial period (Fig. 1).

Body weight

Throughout the study, there was an overall increase in body weight for all groups from 0 - 35 dpi. The body weight of chickens in group C was 685.20±25.69g on day 14 which was statistically higher ($P<0.05$) than that of other groups. There was no significant difference ($P>0.05$) in body weight for all groups at 28 and 35 dpi. There was also no significant difference ($P>0.05$) in body weight for chickens in the challenged groups. After the challenge, the non-booster group (A) decreased by 11.59%, the booster group (B) increased by 4.57%, while the control group (C) remained the same (Fig. 2).

Bursa of fabricius weight

The weight of the bursa increased progressively in all the groups throughout the study. However, the bursa weight was 2.51±0.12g which was lower ($P>0.05$) than 2.72±0.73g and 2.78±0.33g recorded by chickens in groups A and B respectively. The weight of the bursa of challenged chickens in groups A and B were 3.13±0.78g and 4.00±1.27g, respectively which were higher ($P>0.05$) than 2.89±1.04g recorded by the control chicken group. After the challenge, the bursa weight for the non-booster group (A) decreased by 19.02%, the booster group (B) increased by 27.82% and the control group (C) decreased by 20.53% (Fig. 3).

Bursa-to-Body-Weight ratio

The bursa-to-body-weight ratio decreased among chickens in all groups from 0 to 35 dpi. The bursa-to-body-weight ratio of the control chickens was 1.42±0.10 which was not significantly different ($P>0.05$) from 1.63 ±0.26 and 1.39±0.14 of the groups A and B respectively.

Fig. 1: Normal clinical signs of chickens. (a) Group C, day 0 pi. (b) Group A, day 14 pi. (c) Group B, day 28 pi. (d) Group C, day 35 pi. (e) Group B, day 35 pi (CH).

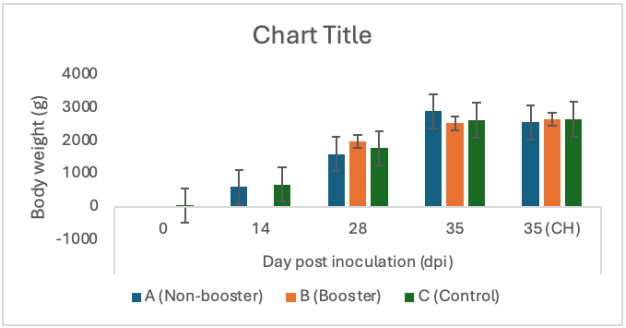

Fig. 2: Body weight of chickens throughout the trial.

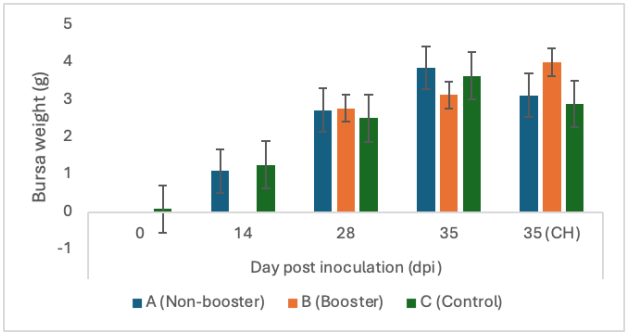

Fig. 3: Bursa of Fabricius weight of chickens throughout the trial.

After the challenge, the ratio was 1.04±0.33, 1.22±0.27 and 1.50±0.44 for groups C, A, and B respectively which were statistically similar (P>0.05). After the challenge, the bursa-to-body-weight ratio for the non-booster group (A) decreased by 7.48%, the booster group (B) increased by 21.10% and the control group (C) decreased by 24.73% (Fig. 4).

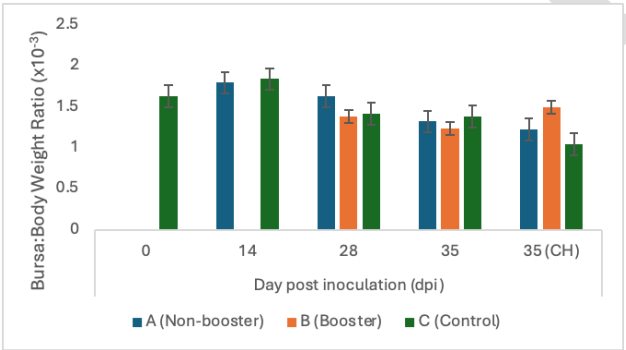

Fig. 4: Bursa-to-body-weight ratio of chickens throughout the trial.

Gross lesions

No abnormal gross lesions were observed in the bursa of Fabricius of all the unchallenged groups from day 0 to day 35 (Fig. 5-7). However, there were enlarged, oedematous, and yellowish bursa lesions observed in the challenged control (CCH) and challenged non-booster (ACH) groups. These pathological changes were more severe in CCH than in the ACH groups (Fig. 8).

Bursal lesions and lesion scoring

The bursal lesion for all groups A, B, and C remained normal to mild, lesion scoring ranged from 0.20 to 0.80 from day 0 to day 35 (Fig. 9). There was no significant difference in bursal lesion scoring among all groups from day 14 to day 35. After the challenge, the lesion scoring of the bursa of the booster group on day 35 was significantly lower (P<0.05) than that of the non-booster and control groups. After challenge, the bursa lesion scoring of the control challenged group ranged from moderate-severe to severe (4.40±0.24), while the challenged group A and B were moderate-severe to severe (4.20±0.20) and mild-moderate to moderate (2.8±0.80), respectively (Fig. 10 and 11).

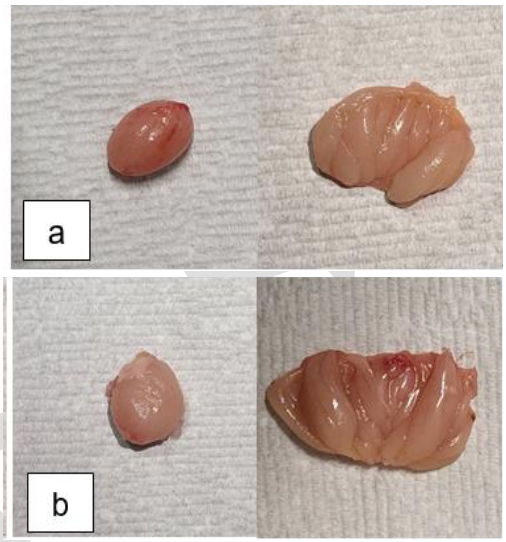

Fig. 5: Gross lesion of the bursa of Fabricius of the chickens on day 14pi. (a) Group C. (b) Group A.

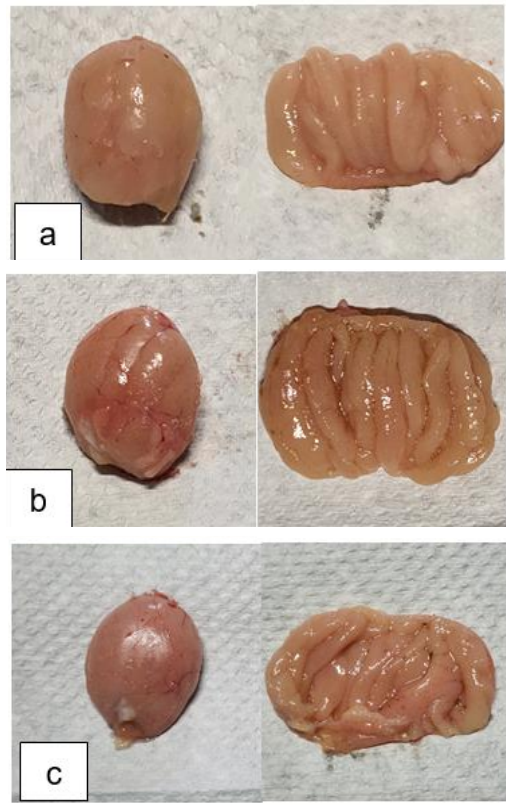

Fig. 6: Gross lesion of the bursa of Fabricius of the chickens on day 28pi. (a) Group C. (b) Group A. (c) Group B.

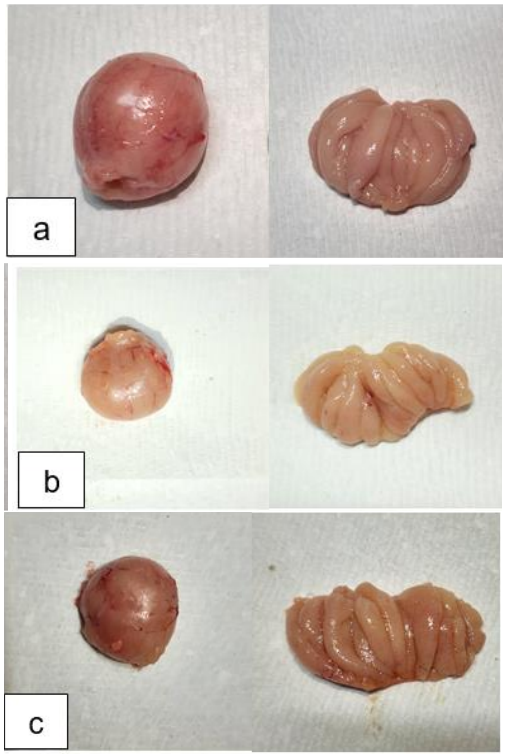

Fig. 7: Gross lesion of the bursa of Fabricius of the chickens on day 35pi. (a) Group C. (b) Group A. (c) Group B.

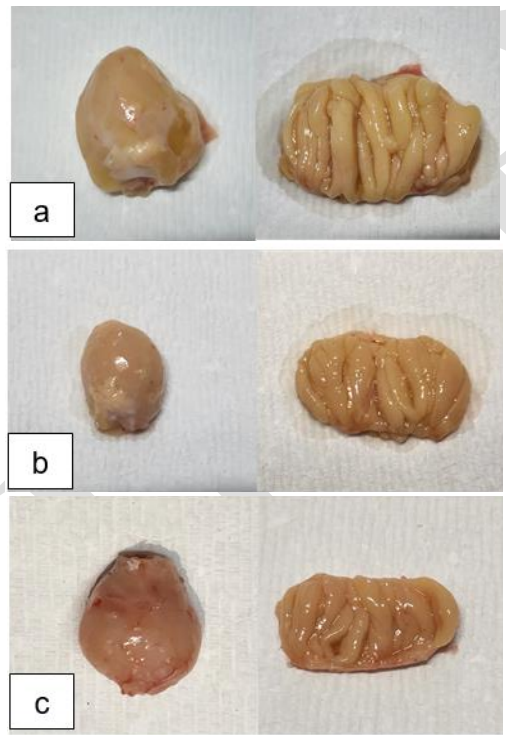

Fig. 8: Gross lesion of the bursa of Fabricius of the chickens post-challenged on day 35pi. (a) Group CCH. (b) Group ACH. (c) Group BCH.

IBD antibody titer

The antibody titer on day 0 pi was 3547±556 ELISA unit. However, there was an overall decrease in the antibody titer of all the groups throughout 35 days. There was no significant difference (P>0.05) in the antibody titer for all groups from day 14 to day 35pi. When comparing pre- and post-challenged groups on day 35, there was also no significant difference (P>0.05) for all groups. The antibody titer of the control challenged chicken was 1801±1425 (ELISA units) which was higher (P>0.05) than that of the challenged chickens in groups A and B (Fig. 12).

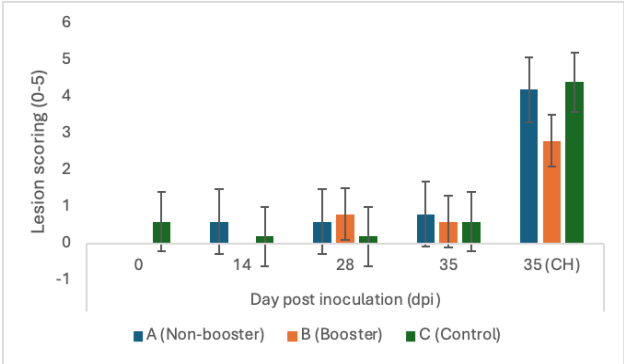

Fig. 9: Bursal lesion scoring of the chickens throughout the trial.

Viral loads and viral shedding

The copy number of the vvIBDV challenge virus in the bursa sample expressed in $\log_{10}$ was 8.865, 8.580, and 8.344 for groups A, B, and C, respectively. In the cloaca, the copy numbers were 8.468, 7.141, and 8.129 for groups A, B, and C respectively (Fig. 13). The chickens in booster group B recorded lower virus shedding than non-booster group A and control group C.

DISCUSSION

vvIBDV infections have a highly devastating effect on the poultry industry worldwide, leading to heavy economic losses (Gao et al. 2024). To ameliorate this, the development of an efficacious vaccine against this disease has become imperative, since the available vaccines do not always provide adequate protection.

The binary ethylene inime (BEI) completely inactivated the virus shown by the inactivated vvIBDV's inability to cause embryonic mortality of SPF eggs. BEI has been reported not to limit the antigenic properties of viruses (Delrue et al. 2012) and has been used in other poultry viruses (Ugwu et al. 2024). On the other hand, the adjuvant used, Montanide 71VG is known to support inactivated viruses maintain long-lasting immunity (Ugwu et al. 2024), which will be useful in the control of vvIBDV infection in chickens.

Although no clinical signs were observed among the control-challenged chickens unexpectedly, it has been reported that experimental infections do not always yield clinical manifestations similar to natural infections (Burrell et al. 2017). Under natural conditions, chickens infected with vvIBDV would show clinical signs that may include inappetence, feather-ruffling, depression, diarrhea, and death (Huang et al. 2021). The absence of clinical signs among the vaccinated unchallenged chickens is an indication of vaccine safety and tolerance in the chickens. Among the vaccinated challenged chickens, no clinical signs were observed. This could be due to the candidate vaccine being efficacious in providing immunity to the chickens, halting the development of the clinical disease.

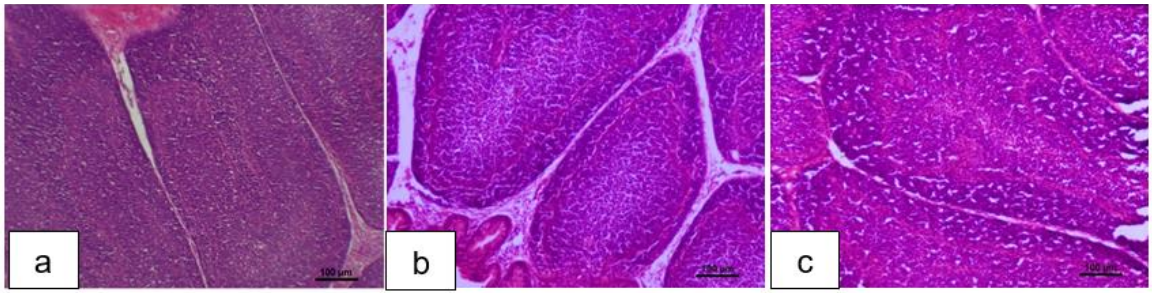

Fig. 10: Histological lesion of the bursa of Fabricius of the chickens on day 35pi. (a) Group C (score 0). (b) Group A (score 1). (c) Group B (score 0). HE, Bar=100µm.

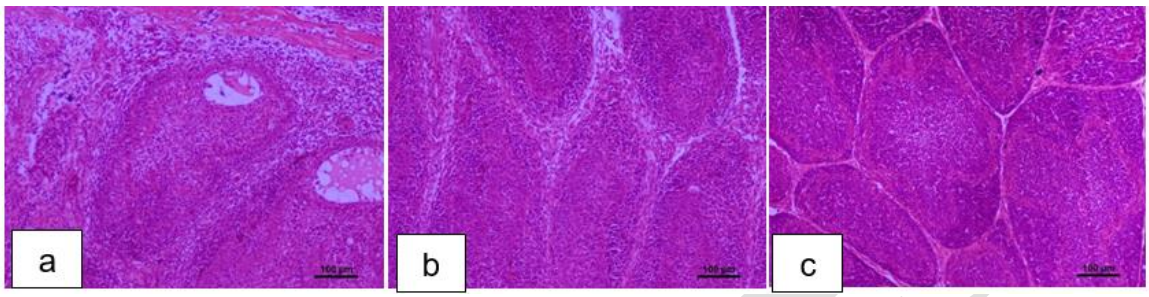

Fig. 11: Histological lesion of the bursa of Fabricius of the chickens post-challenged on day 35pi. (a) Group CCH (score 5). (b) Group ACH (score 3). (c) Group BCH (score 1). HE, Bar=100µm.

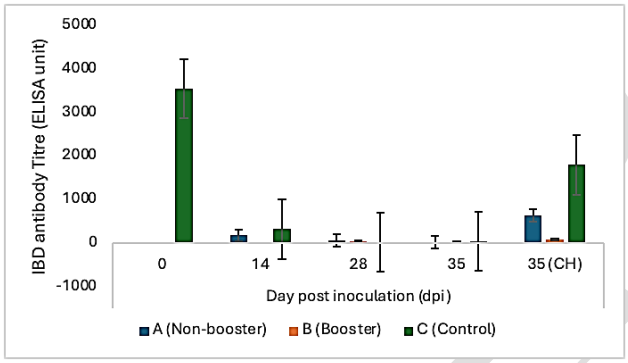

Fig. 12: IBD antibody titer of the chickens throughout the trial.

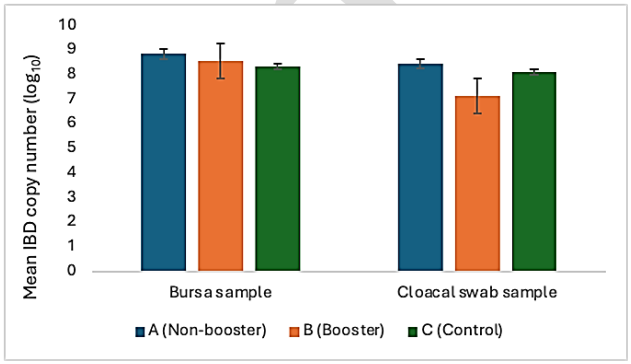

Fig. 13: Viral loads and viral shedding on day 35pi or day 7 post-challenged of the challenged groups.

All chickens in the groups had a progressive increase in their body weight from day 0 to day 35 indicating the safety of the candidate vaccine and showing that the vaccine did not retard the growth performance of chickens. However, the control group had a significantly higher ($P<0.05$) body weight than the non-booster group C at 14 dpi. Ideally, the chickens infected with vvIBDV would have decreased body weight, especially at 4 to 5 dpi (Huang et al. 2021), but the vaccinated chickens recovered. It was also shown that there was no significant difference in the body weight of the inoculated and the control chickens at other time points showing that the inactivated vvIBDV was safe and well tolerated. After the challenge with the pathogenic field strain, the non-booster group (A) had a decreased body weight. In contrast, the booster group (B) recorded an increase in body weight. This means that vaccination with a booster dose would provide better protection than a single dose. The progressive increase in bursa weight throughout the trial reinforces the candidate vaccine as safe and incapable of inducing bursal lesions and atrophy. The bursa of Fabricius serves as the primary lymphoid organ of chicken. vvIBDV infection would naturally cause the bursa to atrophy and become one-third of its original weight or even less (Eterradossi and Saif 2008). The control-challenged chickens recorded a decrease in the bursa weight while the challenged-booster group recorded an increase indicating an improved protection with a booster dose than a single dose. However, the bursa: body weight ratio is the best indicator of bursal atrophy in chickens (Raji et al. 2017; Aliyu et al. 2022). The bursa: body weight ratio of chickens in the control challenged group was lower than those of the vaccinated chickens showing that the pathogenic vvIBDV caused atrophy of bursa in the control chickens. This shows that the vaccinated chickens in groups A and B were protected from bursa lesions associated with vvIBDV, and since the challenged booster group had a better ratio, the booster inoculation could prove more efficacious than a single dose.

Among the non-challenged chickens, no abnormal gross lesions were observed on the bursa and other organs among the groups from day 0 to day 35 indicating that the candidate vaccine was safe. However, the challenged chickens in the non-booster and control groups recorded

abnormal gross lesions in the bursa of Fabricius. Enlarged, oedematous and yellowish bursas; haemorrhages at the junction of proventriculus and gizzard, as well as haemorrhages on skeletal muscles are indicative of positive infections of vvIBDV (Stoute et al. 2009). Meanwhile, no abnormal gross lesions were observed among chickens in the booster group which again suggests that the booster inoculations may provide better protection than a single dose. Furthermore, the absence of histopathological changes among the non-challenged chickens in groups A, B, and C with lesion scoring of 0-1, indicates that the inactivated vvIBDV with Montanide 71VG is safe and non-pathogenic to chickens. Lesion scoring is used to measure the severity of infections and tissue damage (Hair-Bejo et al. 2000). Hence, the safety of the candidate vaccine in terms of not causing bursal lesions was proven. The bursal lesion scoring of the control challenged group (CCH) post-challenge ranged from moderate-severe to severe, indicating a positive vvIBDV infection but that of the booster group (BCH) was from mild-moderate to moderate. This shows that a booster dose could better protect the bursa and prevent immunosuppression.

The chickens in this trial had high antibodies at 0 dpi indicating the presence of maternally derived antibodies. Maternal antibodies could have a half-life of about 5.5 days (Al-Natour et al. 2004) and could also persist in the chicken for 18 to 21 days (Ugwu et al. 2024). This is consistent with the findings in this study, whereby there was a drop of antibody titer in all groups from day 14 onwards. Under field situations, the waning of maternal antibodies would cause the chick to be more susceptible to infection (Zaheer and Akhter 2003). Usually, chickens infected with vvIBDV would have a rise in the mean ELISA titer between 21 and 28 days and peak at 35 days (Gardin et al. 2009). In this study, after being challenged with the pathogenic field strain of vvIBDV, the results showed that the control group (CCH) had the highest increase in the antibody titer, indicating a higher vvIBDV replication. The lower antibody response especially with the booster group could be an indication that the virus could not replicate much to induce antibody production.

The findings showed that there was no significant difference in the viral load of vvIBDV in the bursa which shows that the pathogenic strain may not have protected the chickens from virus replication. But it seems that the presence of the virus in the bursa of the vaccinated chickens did not lead to histopathologic changes in the bursa which is difficult to explain and requires further studies. However, the booster dose recorded lower shedding which is a positive sign of vaccine efficacy (Miller et al. 2009). This has highlighted the importance of booster doses in the inactivated vvIBDV efficacy in broiler chickens.

Conclusion

vvIBDV was completely inactivated with BEI and mixed with Montanide 71VG to produce inactivated vvIBDV candidate vaccine. The inactivated vvIBDV in this study was inoculated into commercial broiler chickens at day old and did not produce any adverse effects on the chickens but protected the chickens from the pathogenic vvIBDV infection. The inactivated vvIBDV with Montanide 71VG is safe, and efficacious, and could be used as a potential candidate vaccine against vvIBDV infections in broiler chickens with a booster dose.

Funding: This study was funded by the University Putra Malaysia, grant number vot. 6300899.

Competing interests: The authors declare no conflict of interest.

Data Availability Statement: The data that supports the findings of this study are available in the material of this article. There is no other supporting data.

Author's Contribution: Mohd Hair Bejo acquired the Funds, conceptualized and supervised the work; and read the manuscript. Chang Zhi Ning, Mazlina Mazlan, Norfitriah Mohamed Sohaimi, and Chidozie Clifford Ugwu conducted the experiments, collected and analyzed the data; and prepared the manuscript. All authors read and approved that last manuscript version.

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