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# Comparative Efficacy of Different Fixed Drug Combinations on Clinical Signs of Respiratory Disease in Starter Pigs

## (PERBANDINGAN KHASIAT KOMBINASI OBAT TERHADAP GEJALA KLINIS PENYAKIT PERNAPASAN BABI STARTER

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## ABSTRACT

The high occurrence of respiratory disease in pigs has led to the innovation of fixed-dose drug combinations (FDCs). A study was conducted to determine the efficacy of two FDCs on 15 starter pigs showing clinical signs of respiratory disease to determine its effect on their respiratory health and growth. Treatment 1 (T1) was the control group and did not receive any medication. Treatment 2 (T2) contains 90 g of Doxycycline, 40 g of Tylosin, 30 g of Paracetamol, 5 g of Bromhexine, and 500 mg of Prednisolone as active ingredients per kilogram. Treatment 3 (T3) contains 150 g of Amoxicillin Trihydrate, 100 g of Tylosin Tartrate, and 5 g of Bromhexine Hydrochloride as active ingredients per kilogram. The treatment gives at a therapeutic dose of 10 g/gallon of water twice a day for 7 days.The effects of FDCs were measured through clinical sign evaluation, gross pathologic lung lesion scoring, histopathologic examination, and evaluation of the production performance of the starter pigs using analysis of variance (ANOVA) for a Completely Randomized Design.. Pigs treated with Treatment 2 had better clinical evaluation scores and production performance than Treatment 3. Histopathologic examination demonstrated minimal tissue repair in all FDCs studied. Improvement denotes that the treatment produces a positive effect.

Keywords: antibiotics; fixed-dose drug combination; lung lesion scoring; starter pigs; respiratory disease.

## ABSTRAK

Tingginya kejadian penyakit saluran pernapasan pada babi telah mendorong lahirnya inovasi kombinasi obat dosis tetap (*fixed-dose drug combination*/FDCs). Penelitian INI dilakukan bertujuan untuk menentukan kemanjuran dua FDC pada 15 ekor babi pemula/*starter* yang menunjukkan tanda-tanda klinis penyakit pernapasan untuk menentukan pengaruhnya terhadap kesehatan pernapasan dan pertumbuhan para babi percobaan. Perlakuan yang diberikan berupa Perlakuan-1 (T1) adalah kelompok kontrol dan tidak menerima pengobatan apa pun. Perlakuan=2 (T2) mengandung 90 g Doxycycline, 40 g Tylosin, 30 g Paracetamol, 5 g Bromhexine, dan 500 mg Prednisolon sebagai bahan aktif per kilogram. Perlakuan-3 (T3) mengandung 150 g Amoksisilin Trihidrat, 100 g Tylosin Tartrate, dan 5 g Bromhexine Hydrochloride sebagai bahan aktif per kilogram. Perlakuan diberikan dalam dosis terapi 10 g/galon (1 galon= 4,546 L) air, sebanyak dua kali sehari selama tujuh hari. Pengaruh FDC diukur berdasarkan hasil evaluasi terhadap tanda klinis, scoring lesi patologi anatomi paru, pemeriksaan histopatologi, dan evaluasi terhadap kinerja produksi babi-babi *starter* menggunakan analisis varians atau sidik ragam dalam Rancangan Acak Lengkap. Babi-babi yang diobati dengan Perlakuan-2 memiliki skor evaluasi klinis dan kinerja produksi yang lebih baik daripada Perlakuan-3. Pemeriksaan histopatologi menunjukkan perbaikan jaringan minimal ditemukan pada semua FDC yang diteliti. Perbaikan menunjukkan bahwa pengobatan menghasilkan efek positif.

Kata-kata kunci: antibiotik; kombinasi obat dosis tetap; *fixed-dose drug combination*; skoring lesi paru; babi-babi *starter;* penyakit pernapasan

## INTRODUCTION

Respiratory disease is considered to be the most economically important health concern that affects pigs. Besides the effect that it causes on the respiratory tract, it also greatly affects the feed intake, subsequently, the growth of the pigs (Nathues *et al*., 2017) and contributes adversely to morbidity and mortality, increased use of antimicrobials, poor pig welfare and reduced productivity (Cohen *et al*., 2020). In a farm setting, there is a high probability of respiratory disease outbreaks occurring and resulting deaths are inevitable. Even if pigs afflicted with respiratory diseases can survive, they will exhibit a reduction in feed conversion efficiency and a decrease in meat quality. Also, these recovered pigs may retain the pathological lesions of their infection and would affect the sale of their meat at slaughter (Sarli *et al*., 2021; Pessoa *et al*., 2020). Pleuritis is a common finding in swine at slaughterhouses; chronic fibrous pleuritis is associated with serologic positivity to *Actinobacillus pleuropneumoniae* and is concluded to be the etiology in most cases, particularly those with a dorsocaudal pleural surface involvement (Merialdi *et al*., 2012).

Total elimination of respiratory diseases seems far-fetched, especially when dealing with multiple animals, like the ones in swine farms, but prevention of the spread of respiratory disease outbreaks may be possible by proper management. Better biosecurity may help to improve productivity and may contribute to reducing the use of antibiotics. This includes strict biosecurity measures with appropriate medication programs (Alarcón *et al*, 2021; Toya *et al*., 2021). The use of drugs in animals has raised concerns about increasing antimicrobial resistance (Lekagul et al, 2019). Therefore, the minimization of antimicrobial use in livestock is necessary to reduce the risk of selection pressure (FAO, 2015). One of the many innovations that are favored nowadays is the use of fixed-dose drug combinations (FDCs). Drug combinations are greatly becoming popular in the animal industry because of the many benefits it provides. According to Bell (2013), potential advantages of drug combination preparations are increased compliance, synergy, increased efficacy, and reduced side effects and cost. Potential disadvantages, on the other hand, are an inflexible fixed-dose ratio, incompatible pharmacokinetics, increased toxicity, and cost (Balat *et al*., 2014).

It has been hypothesized that the reason for the emergence of new FDCs is that the products sold nowadays are showing lesser therapeutic effects than when the drugs were initially marketed. In the Philippines, the use of antibiotics at sub-therapeutic levels as growth promotants is practiced. This controversial method has led researchers to believe that antibiotic resistance is inevitable with the medicines that are presently available for animals (Bengtsson and Greko, 2014). For this reason, it is time to find an alternative solution on how to improve the health of food animals.

The use of farm-grade veterinary antibiotics, as part of fixed-dose drug combinations which contain two or more active substances within a single dosage form, in treating pigs afflicted with respiratory disease is recommended, mostly because of its economic benefits and reduce the lengthy timeline (Wushouer *et al*., 2022). Doxycycline-Tylosin-Paracetamol-Bromhexine-Prednisolone is a combination of a tetracycline antibiotic, a macrolide antibiotic, an antipyretic, an expectorant, and an anti-inflammatory agent. No FDC with the same drug combination has been marketed. Nevertheless, with the characteristics of the drugs combined in Doxycycline-Tylosin-Paracetamol-Bromhexine-Prednisolone, it was a likely candidate for an effective FDC. Amoxicillin-Tylosin-Bromhexine, on the other hand, is a combination of an aminopenicillin, a macrolide antibiotic, and an expectorant. Given the properties of the Amoxicillin-Tylosin-Bromhexine combination and its availability, it was a candidate for the comparison of effective FDCs. In the study, the two fixed-dose drug combinations were used in order to compare their efficacy in the treatment of respiratory disease and the effect that the drugs would impose on the production performance of the starter pigs.

## RESEARCH METHODS

### Animals

Fifteen pigs of mixed sexes aged three months old with Landrace x Large White x Duroc breed naturally showing clinical signs of respiratory disease were obtained from a commercial swine farm (Maahas Farm). The pigs were weighed upon arrival and randomly assigned to three treatments following a Completely Randomized Design. The pigs were housed at the experimental swine farm of

Veterinary Teaching Hospital- Maahas Station at Los Baños, Laguna. Animal care and use in this experimentation was carried out in accordance with all applicable institutional, local, and national guidelines with the approval of the Institutional Animal Care and Use Committee (IACUC) assigned protocol number: 2017:0008..

**Treatments Used**

Treatment 1 (T1) was the control group and did not receive any medication. Treatment 2 (T2) contains 90 g of Doxycycline, 40 g of Tylosin, 30 g of Paracetamol, 5 g of Bromhexine, and 500 mg of Prednisolone as active ingredients per kilogram. The recommended treatment dosage is ten grams per gallon of drinking water orally for five to seven days. The withdrawal period is ten days for swine. Treatment 3 (T3) contains 150 g of Amoxicillin Trihydrate, 100 g of Tylosin Tartrate, and 5 g of Bromhexine Hydrochloride as active ingredients per kilogram. The recommended treatment dosage is ten grams per gallon of drinking water orally for five days. The withdrawal period is seven days for swine.

**Diet**

Water troughs were used for the dispensing of the FDCs. For T2 and T3, the water troughs were filled with doses equal to ten grams per gallon of Doxycycline-Tylosin-Paracetamol-Bromhexine-Prednisolone and ten grams per gallon of Amoxicillin-Tylosin-Bromhexine after morning and afternoon feed rations of specifically formulated hog starter feeds.

**Experimental Procedure**

Three treatments were used in the study following a Completely Randomized Design. Four replicates were allocated for T1, six replicates were allocated for T2, and five replicates were allocated for T3. Before the start of the experiment, the weight of each pig was measured (28.81±1.17kg). The feed intake was recorded on a per pen per day basis for all treatment groups. Throughout the experimentation period, Total Feed Consumed (TFC), Average Daily Gain (ADG), and Feed Conversion Ratio (FCR) were recorded for all treatment groups. The average daily gain was calculated as the initial weight minus the final weight divided by the number of experimental days. Feed conversion ratio was calculated as TFC divided by ADG. The weights of the pigs at the end of the experiment were also recorded and Total Body Weight Gain (TBWG) was computed.

Grading of the respiratory system expulsion reflex, type and quality of nasal discharge, type and quality of ocular discharge, hair coat quality, and type and quality of breathing was assessed upon arrival once the randomization and allocation per treatment were carried out (Gallardo *et al*., 2015). Respiratory System Expulsion Reflex Grading System (0=No reflex; 1=Sneezing; 2=Mild coughing; dry or unproductive; 3=Moderate coughing to severe; dry or unproductive; 4=Severe coughing. Type and Quality of Nasal Discharge Grading System (0=No discharge; 1=Mild; serous;2=Moderate; serous to purulent; 3=Severe; muco-purulent type of discharge). Type and Quality of Ocular Discharge Grading System; 0=No discharge; 1=Mild; serous; 2=Moderate; serous to purulent; 3=Severe; muco-purulent type of discharge. Hair Coat Quality Grading System (0=Normal hair coat; 1=Rough and raised; 2=Raised and thickened; 3=Clumpy type of hair coat. Type and Quality of Breathing (0=Normal; 1=Labored or abdominal breathing; 2=Dyspneic).

The FDCs were administered via drinking water twice every day for a seven-day experimental period. The grading of clinical signs observed was done every day for at least three hours to maximize the observations that may be noted all throughout the experiment. Three randomly selected pigs per treatment were sacrificed after the experiment. Examination of the lungs grossly was done and gross pathologic lung lesion scoring was performed. Lung specimens were collected for histopathologic examination.

The livability and frequency of the observed respiratory clinical signs were also recorded. The data collected were tabulated and presented.

**Clinical Disease Evaluation**

1. **Frequency of the respiratory clinical signs**
   All the animals in the study were monitored for clinical signs of sickness associated with diseases that affect the respiratory system. The number of morbid animals showing the specific respiratory clinical sign grading in the group was recorded as the frequency.
2. **Respiratory clinical sign scoring**
   The respiratory expulsion reflex, type and quality of nasal discharge, type and quality of ocular discharge, hair coat quality and type and quality of breathing were recorded in the duration of the seven-day experimental period. Only the researcher was in charge

of recording the observations to maintain uniformity (Gallardo et al., 2015).

3. **Number of animals showing respiratory clinical signs**
4. **Percent of improvement from clinical signs of respiratory disease** was calculated with the formula:
   Percent improvement= 1-(final clinical sign score/initial clinical sign score) x 100
5. **Gross Pathologic Lung Lesion Grading System**
   The Basic "55" lung lesion scoring system, bronchopneumonia lesion scoring, quantification of scarring, cranial pleurisy scoring, and dorso-caudal pleurisy scoring were performed and recorded (CEVA and IZLER, 2012; Sibila et al., 2014).
6. **Histopathologic lesion scoring**
   Histopathologic lesions were interpreted and recorded. Histopathologic markers of tissue repair were used to determine the efficacy of the FDCs. These markers are type II pneumocyte proliferation, alveolar edema reabsorption, reduction of inflammatory response, and presence of collagen fibers, which could be observed during the repair phase of lung tissue injury (Gonzalez-Lopez and Albaiceta, 2012).

**Production Parameter Evaluation**

The initial and final body weight, total body weight gain, average daily gain, feed consumption, average daily feed intake, feed conversion ratio, and livability were recorded and summarized.

**Data Analysis**

The data on respiratory health and production parameters were subjected to analysis of variance (ANOVA) for a Completely Randomized Design using the Kruskal-Wallis H test and Wilcoxon-signed rank test for clinical disease parameters, Wilcoxon-Mann/ Whitney test for Total Body Weight Gain, Welch test and Dunnet T3 test for Average Daily Gain, and Scheffe test and LSD test for Feed Conversion Ratio. All tests utilized the IBM SPSS Statistics Software.

## RESULTS AND DISCUSSION

Effect of the different treatments on the respiratory health status of pigs by clinical sign evaluation. Diagnosis and severity estimation of respiratory disease in pig herds is achieved through clinical examination and post-mortem examinations of dead or euthanized animals during farm visits, and routine slaughter checks (VanAlstine, 2012).

Because of the high occurrence of respiratory disease, one of the many innovations that are favored is the use of fixed-dose combinations (FDCs). FDCs are greatly popular in the animal industry because of the many benefits it provides and has been widely successful in the treatment

Table 1. Percent improvement of the clinical signs evaluated of the starter pigs per treatment group during the seven days experimental period.

| Percent Improvement (%) | Treatment 1 | Treatment 2 | Treatment3 |
|---|---|---|---|
| Respiratory system expulsion reflex | 0 | 78.54 | 66.67 |
| Nasal discharge | 20 | 85.47 | 75 |
| Ocular Discharge | 20 | 74.63 | 75 |
| Hair coat quality | -100 | 78 | 50 |
| Breathing type and quality | 0 | 62.41 | 33.33 |

Table 2. Resolution value from clinical signs evaluated of the starter pigs per treatment group during the seven days experimental period.

| Resolution value | Treatment 1 | Treatment 2 | Treatment3 |
|---|---|---|---|
| Respiratory system expulsion reflex | 0 | 4 | 2 |
| Nasal discharge | 0 | 5 | 3 |
| Ocular Discharge | 0 | 5 | 5 |
| Hair coat quality | 0 | 4 | 2 |
| Breathing type and quality | 0 | 4 | 3 |

of asthma and chronic obstructive pulmonary disease (Brunaugh *et al.*, 2021). T2 and T3 are examples of FDCs.

The pigs that received T2 showed a higher percent improvement for all clinical sign grading systems than pigs that received T3, with the exception of the ocular discharge clinical sign. As shown in Table 1, nasal discharge characteristics that were graded had the highest percent improvement for T2 and T3. Breathing type and quality, on the other hand, had the lowest percent improvement for T2 and T3.

Resolution of clinical signs is an important factor in assessing the efficacy of a drug. As presented in Table 2, nasal and ocular discharge had the fastest resolution for T2 compared to other clinical signs graded. T3 had a slower resolution compared to T2, having nasal discharge and breathing type and quality as its fastest resolution values. Tables 3 shows the gross pathologic lung lesion scores of the starter pigs per treatment group as observed during the 7-day experimental period.

As presented in Table 3, following the recommendations of White (2017), with the Basic "55" scores over 10 in all experimental groups, it is assumed that absolute resolution of the disease was not achieved and herd medication is necessary. In the experiment, the incidence of scarring was minimal, it was found in only one sample for T1, one sample for T3, and was non-existent for T2 (Table 3). This strengthens the possibility of the presence of *Mycoplasma hyopneumoniae* in the experimental herd, but in this case, as a chronic infection.

As shown in Table 3, T2 and T3 have comparable data on bronchopneumonia lesions. Since the test screens for the possibility of *M. hyopneumoniae* being the pathogen involved in the disease process of the experimental pigs, it is safe to assume that the said organism is one of the pathogens that affected the experimental herd. To know the real prevalence of lesions associated with M. hyopneumoniae infection as well as to highlight the use of histopathology to confirm the lesions (Pallarés *et al*, 2021).

As presented in Table 3, the presence of cranial pleurisy in the experimental herd warrants various respiratory pathogens. Dorso-caudal pleurisy, on the other hand, denotes that the sample observed in T2 was most probably an Actinobacillus pleuropneumoniae infection since dorso-caudal pleurisy is a SPES indication for the disease caused by the said pathogen (Ceva and Izler, 2012).

With the screening procedures for gross pathologic lung lesion scoring, it was established that majority of the samples scored have *Mycoplasma hyopneumoniae*-like and *Actinobacillus pleuropneumoniae*-like lesions with varying severities. Lesions in the respiratory tract were registered according to rules set by The Swedish Food Administration (SLVFS 1996:32 and SLVFS 2002:27). Adhesions between lungs and pleura intercostalis larger than 10 cm2 (a diameter of 3.5 cm) were recorded as pleuritis. Ongoing pneumonic lesions in the cranio-ventral parts of the lungs were recorded as *Mycoplasma*-like pneumonia. Acute pneumonic lesions in other parts of the lung were registered as A. *pleuropneumoniae*-like pneumonia (Wallgren *et al.*, 2016).

As lifted from the study of Gonzalez-Lopez and Albaiceta (2012), type II pneumocyte proliferation, alveolar edema reabsorption, reduction of an inflammatory response, and presence of collagen fibers are the histopathologic markers that could be observed during the repair phase of lung tissue injury. The sickness response is caused by increased inflammatory mediators (Saper *et al.*, 2012). Inflammatory pathways impact the pathogenesis of a number of chronic diseases, and involve common inflammatory mediators and regulatory pathways. Inflammatory stimuli activate intracellular signaling pathways that then activate production of inflammatory mediators (Chen *et al.*, 2018).

Table 3. Means of the gross pathologic lung lesion scores of the starter pigs per treatment group for seven days

| | Treatment 1 | Treatment 2 | Treatment 3 |
|---|---|---|---|
| Basic 55 Scoring System | 45±8.66 | 36.67±16.07 | 30±13.23 |
| Bronchopneumonia lesions | 3±0.00 | 2.33±1.53 | 2.33±0.58 |
| Quantification of lung scarring | 0 | 0 | 0 |
| Cranial pleurisy scoring | 0.67±0.58 | 0.67±0.58 | 1±0.00 |
| Dorso-caudal pleurisy | 0 | 1±1.73 | 0 |

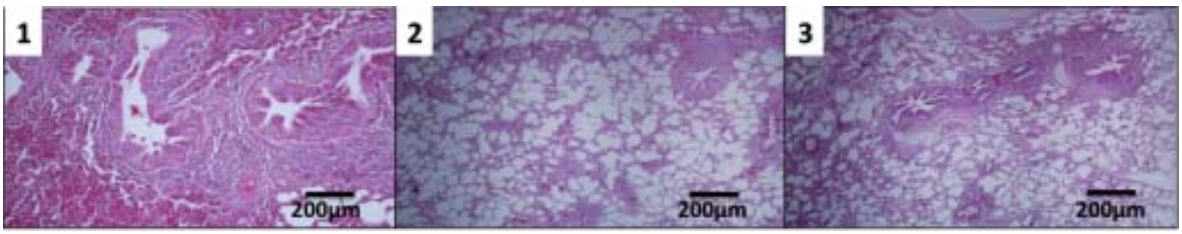


Figure 1. Histopathologic comparison of lung samples taken from the starter pigs at the end of the seven days experimental period using hematoxylin & eosin stain. (1) Treatment 1, (2) Treatment 2, (3) Treatment 3.

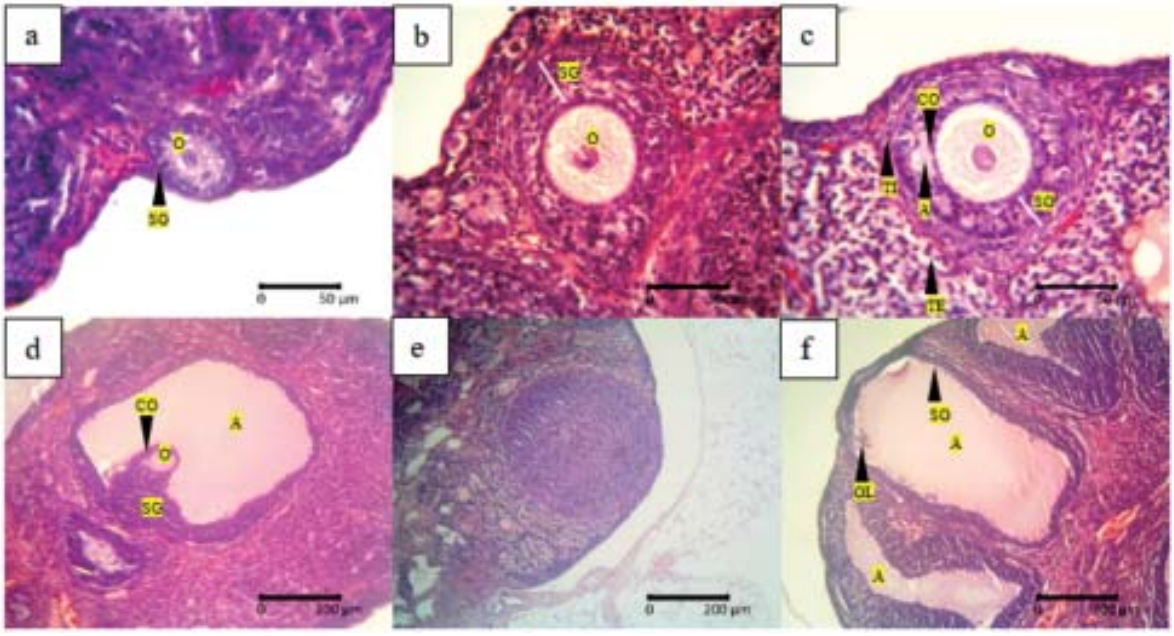


Figure 2. Histopathologic comparison of lung samples taken from the starter pigs at the end of the 7-day experimental period using hematoxylin & eosin stain. (1) Treatment 1, red blood cell and inflammatory cell infiltration evident. Flooded alveolar spaces with disruption of alveolar epithelium and damaged alveolar capillary endothelium. (2) Treatment 2, collagen (black circle), fibrin and cuboidal type II pneumocytes (black arrows) are evident. (3), Treatment 3. Collagen (black circle), fibrin and cuboidal type II pneumocytes (black arrows) are evident.

T1 samples showed bronchopneumonia lesions with grave severity. The normal lung pathology was obliterated. The alveolar air spaces were flooded; there was disruption of the alveolar epithelium, damage to the alveolar-capillary endothelium, and the presence of red blood cells and inflammatory cell infiltration. No improvement in lung tissue was seen in the animals from which the histopathologic samples were taken (Figs. 1 and 2).

For samples taken from pigs that received T2 and T3, although mild inflammatory cell infiltration and edema were observed, the presence of collagen and fibrin strengthens the claim that the lungs of the starter pigs of which the samples were obtained form show tissue repair, which is attributed to the repair phase of lung tissue injury. Type II pneumocytes are characteristically cuboidal in nature, and the presence of these particular cells lining the alveoli, again, supports that tissue repair is evident (Gonzalez-Lopez and Albaiceta, 2012). Although the alveolar air spaces are mild-moderately filled by inflammatory infiltrates, it can be assumed that T2 and T3 presented tissue repair and that minimal efficacy of the Doxycycline-Tylosin-Paracetamol-Bromhexine-Prednisolone FDC was observed on the animal

Table 4. Means of the production performance of the starter pigs per treatment group for seven days.

| Production Parameters | Treatment 1 | Treatment 2 | Treatment 3 |
|---|---|---|---|
| Initial weight, Kg | 28.75±2.21 | 27.67±5.88 | 30±4.64 |
| Final weight, Kg | 31.25±2.63 | 32.17±6.61 | 33.4±4.56 |
| Total Body Weight gain, Kg | 2.5±1.29 | 4.5±1.76 | 3.4±0.55 |
| Average Daily Gain (ADG), g | 357.14±184.43 | 642.86±251.53 | 485.71±78.24 |
| Total Feed Consumed (TFC), kg | 7.5±0.00 | 7.5±0.00 | 7.5±0.00 |
| Average Daily Feed Intake (ADFI), g | 1071.43±0.00 | 1071.43±0.00 | 1071.43±0.00 |
| Feed Conversion Ratio (FCR) | 3.91±2.51 | 1.98±1.00 | 2.25±0.34 |
| Livability (%) | 96±1.33 | 94±2.21 | 95±1.07 |

of which the histopathologic samples were taken from given the histopathologic samples (Figs. 1 and 2).

The effect of different treatments on the production parameters of pigs is presented in table 4. As seen in Table 4, T2 has the largest total body weight gain value, possessing a 1.1 kg and 2 kg difference against T3 and T1, respectively.

Respiratory disease is considered to be the most economically important health concern that affects pigs. Besides the effect that it causes on the respiratory tract, it also greatly affects the feed intake, and subsequently, the growth of the pigs (Muirhead *et al*., 2013). According to PCAARDD (2013), the target ADG should be 545 g. per animal. As expressed in Table 4, only T2 went above this target. FCR is the ratio that measures how efficient the animal is in converting its feed into the desired output. The results of the experiment show that T2 gives a better production efficiency as compared to T3. With the claims of Szatmári *et al*. (2022) that paracetamol was found to prevent anorexia in dogs with bronchiectasis, it can be assumed that the same effect was attributed to the Doxycycline-Tylosin-Paracetamol-Bromhexine-Prednisolone FDC in pigs respiratory disease. This can be explained by lessened depression that could be observed because of the analgesic and antipyretic effects of paracetamol. With respiratory disease-causing depression and inappetence, the effect of lessened depression with paracetamol helps the animal increase its feed intake even if the disease is present. Although not statistically significant, there is a notable distinction between the production parameters of the experimental groups.

## CONCLUSION

It can be concluded that FDCs that contains 90 g of Doxycycline, 40 g of Tylosin, 30 g of Paracetamol, 5 g of Bromhexine, and 500 mg of Prednisolone as active ingredients per kilogram had better clinical evaluation scores and production performance than FDCs contains 150 g of Amoxicillin Trihydrate, 100 g of Tylosin Tartrate, and 5 g of Bromhexine Hydrochloride as active ingredients per kilogram as seen in its effects on the clinical signs, gross pathologic lung lesions, histopathological examination, and production performance of the pigs. Diagnostic results on the gross pathologic lung lesion scoring are questionable since this is only a screening procedure, which makes the parameter subjective.

## SUGGESTION

Despite statistical analysis being majorly insignificant, the notable disparity in the health and production performance results between the experimental groups is still considered relevant. Statistically insignificant data may be caused by the small sample size used in the experiment. It is advised to use a larger sample size in order to fully harness the effects of the treatments. Also, for a more comprehensive data recording, gross lung lesion scoring and histopathological examination of all experimental animals can be done. Bacterial isolation and Polymerase Chain Reaction (PCR) may be incorporated in the study as additional diagnostic parameters to be able to pinpoint the specific disease or pathogen that is present in the experimental animals and to

determine the specificity of efficacy of the experimental drugs used. Although complete resolution was not achieved with the FDCs tested, it should be noted that improvement was observed. Improvement denotes that the treatment produces a positive effect. It is recommended to test different daily administration frequencies or to extend the treatment period to 10 days, rather than 7 days.

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