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Research Article

# Bacteriophage Therapy Reduces Salmonella Infection in Broiler Chickens Under Field Conditions in Indonesia

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**Abstract** | Salmonellosis remains a major constraint in poultry production and a significant public health concern in Indonesia, where contamination of poultry meat with Salmonella enterica is frequently reported and antibiotic-based control strategies are increasingly compromised by antimicrobial resistance. This study evaluated the efficacy and safety of the VAM-S bacteriophage cocktail as an alternative intervention for controlling Salmonella infection in broiler chickens. A controlled field trial was conducted using oral phage administration at two dosages ($10^9$ and $10^8$ PFU/animal) with either weekly or daily regimens. Clinical outcomes, bacterial shedding, intestinal colonization, organ indices, and intestinal histopathology were assessed. Bacteriophage treatment was associated with reductions in cloacal shedding and ileal bacterial load compared to untreated controls, with differences most evident during the early post-treatment period. The $10^9$ PFU regimens showed more consistent reductions, although no clear superiority between dosing schedules was observed. At the final time point, bacteriophage-treated groups showed approximately ~1.0 $\log_{10}$ reduction in cloacal shedding and ileal bacterial load relative to the Negative Control. Clinical observations suggested earlier resolution of symptoms in treated groups. Histopathological Histopathological findings indicated partial preservation of intestinal structure in treated birds. No clear evidence of phage-specific adverse effects on growth performance or tissue integrity was observed; however, liver indices remained elevated in both treated and untreated infected groups, warranting further investigation. These findings indicate that bacteriophage therapy contributes to reducing Salmonella infection in broiler chickens, particularly during the early phase of infection, and support its potential application as a potential alternative to conventional antimicrobial approaches.

**Keywords:** Bacteriophage, Salmonella, Broiler, Efficacy, Safety, Poultry health

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## INTRODUCTION

Salmonellosis poses a major global threat to animal health and public safety, particularly within the poultry industry. The infection, primarily driven by Salmonella enterica serovars like *S. enteritidis* and *S. typhimurium*, inflicts substantial economic damage worldwide through high mortality rates, reduced flock productivity, and imposed trade limitations (Dar *et al.*, 2017; Ismael *et al.*, 2021). These versatile serovars readily colonize the poultry's gastrointestinal and reproductive systems, facilitating vertical transmission through eggs and chicks (Liu *et al.*,

2023; Wigley, 2024). In flocks, the bacteria spread via contaminated feed, water, litter, or direct contact (Betiku *et al*., 2025; Nagara, 2023). While some infected birds exhibit clinical signs like diarrhea, lethargy, and poor growth, subclinical infections are frequent and responsible for the silent, sustained spread of the disease within poultry operations (Wigley, 2024).

From a public health perspective, non-typhoidal *Salmonella* is a major global foodborne pathogen, responsible for approximately 93 million cases of gastroenteritis and 155,000 deaths annually worldwide (Chlebicz and Śliżewska, 2018; Lamichhane *et al*., 2024). Transmission to humans commonly occurs through the consumption of contaminated poultry meat and eggs, with poultry and poultry products representing key vehicles of infection (Eng *et al*., 2015; Tan *et al*., 2022). While symptoms often manifest as self-limiting gastroenteritis, the disease can escalate to severe systemic illness, particularly in vulnerable populations (young children, elderly, immunocompromised) (Eng *et al*., 2015; Mkangara, 2023). Consequently, controlling Salmonella in poultry production represents a priority for global food safety and animal health sectors (Wahyono and Utami, 2018).

In Indonesia, the burden of *Salmonella* contamination in poultry production remains a significant and persistent challenge, with several studies reporting high prevalence rates in retail chicken meat and traditional markets. Recent investigations have identified contamination levels ranging from moderate to high across different regions, reflecting gaps in on-farm biosecurity and post-harvest handling practices (Nissa *et al*., 2023; Shalihah *et al*., 2024; Wardhana *et al*., 2021). In parallel, the emergence of antimicrobial-resistant (*AMR*) *Salmonella* strains in Indonesian poultry systems has been increasingly documented, including multidrug-resistant isolates from broiler meat, raising serious concerns regarding treatment efficacy and public health risks (Fanissa *et al*., 2022). Given Indonesia's strategic objective to expand its poultry product exports, implementing effective and safe control measures against Salmonella on farms is an urgent necessity to enhance both food safety and economic competitiveness (Wahyono and Utami, 2018).

Conventional strategies for controlling Salmonella enterica in poultry are increasingly hindered by the global antimicrobial resistance (AMR) surge, significantly reducing the efficacy of standard antibiotic treatments (Nabil *et al*., 2024; Żbikowska *et al*., 2020). This challenge necessitates the development of novel and sustainable alternatives. A promising solution is the application of bacteriophages, viruses that naturally and specifically target and destroy bacteria (Abd-El Wahab *et al*., 2023; Segundo-Arizmendi *et al*., 2025). Phages work by attaching to the bacterial surface, injecting genetic material, and ultimately causing the host cell to lyse (burst) and release new viral progeny (Atterbury *et al*., 2007; Żbikowska *et al*., 2020). Due to their high host specificity, bacteriophages are generally considered capable of targeting pathogenic *Salmonella* strains, including multidrug-resistant (MDR) variants, with relatively limited impact on commensal gut microbiota compared to broad-spectrum antibiotics, although this aspect was not evaluated in the present study (Hu *et al*., 2018; Khan and Rahman, 2022; Kuang *et al*., 2026; Nabil *et al*., 2024). This precise action minimizes the risk of dysbiosis and supports overall gut health in poultry, establishing phage therapy as a superior alternative or to complement traditional antimicrobial measures (Thanki *et al*., 2023).

Despite the promise of phage therapy, challenges such as the potential development of bacterial resistance remain, and its application against prevalent Salmonella strains in Indonesian poultry is underexplored (Abd-El Wahab *et al*., 2023; Ariyanti, 2018). Therefore, this study aims to evaluate the efficacy and safety of the VAM-S® bacteriophage cocktail as a sustainable control measure against Salmonella in live chickens in Indonesia (SK8 Biotech, 2025). The VAM-S® bacteriophage cocktail used in this study was formulated based on *Salmonella* strains prevalent in Indonesia to ensure targeted antimicrobial activity. The study includes in vivo experiments to comprehensively assess the phages' biological performance, including their safety, colonisation efficiency, and impact on reducing Salmonella loads in broiler flocks. The findings will provide crucial data on the feasibility of integrating phage therapy into routine poultry health management in the Indonesian industry, thereby contributing vital insights toward enhancing food safety and addressing the urgent need for antibiotic-alternative strategies.

## MATERIAL AND METHODS

### Study design

A controlled field trial was conducted controlled housing conditions designed to simulate field-relevant exposure in Indonesia to evaluate the efficacy and safety of a bacteriophage cocktail against *Salmonella enterica* infection in broiler chickens. Although conducted in a controlled housing system, the study design incorporated practical management conditions and oral administration protocols relevant to poultry production, allowing preliminary evaluation of bacteriophage efficacy under field-relevant conditions. A total of 60 clinically healthy broiler chickens (3 weeks old at arrival) were obtained from a commercial source and acclimatized for 7 days prior to the experiment. Following acclimatization, birds were 4 weeks of age at the

time of Salmonella challenge. Birds were maintained under standard husbandry conditions with ad libitum access to feed and water throughout the study period. Chickens were randomly allocated into six experimental groups (n = 10 birds per group) based on treatment regimen and dosing schedule Table 1.

## Salmonella challenge

A pathogenic *Salmonella enterica* isolate derived from field samples was used for the experimental challenge and maintained as a laboratory strain. The isolate was originally identified as *Salmonella Enteritidis*; however, no further serovar confirmation, antimicrobial resistance profiling, or phage susceptibility testing was conducted prior to the study. Birds in Groups 1–5 were orally challenged at 4 weeks of age (defined as Day 0 of infection) with 1 mL of the bacterial suspension $10^7$ colony-forming units (CFU)/mL. The Normal Control group (Group 6) received no bacterial challenge. Baseline bacteriological cultures were performed prior to challenge (Day 0), and all birds tested negative for detectable *Salmonella*. Following oral challenge, bacterial colonization was monitored using cloacal swab and/or fecal culture during the early post-challenge period to confirm successful infection prior to or at the initiation of bacteriophage treatment.

No selective marker (e.g., antibiotic resistance marker) was used to distinguish the challenge strain from potential environmental *Salmonella*. Although no selective marker was used to distinguish the challenge strain from environmental *Salmonella*, several measures were implemented to minimize this risk. Baseline bacteriological cultures confirmed that all birds were negative prior to challenge, and birds were maintained under controlled housing conditions with standardized feed and management practices. The consistent temporal increase in bacterial load following oral challenge further supports successful experimental infection.

## Bacteriophage preparation and administration

The VAM-S® bacteriophage cocktail used in this study consisted of three bacteriophage strains obtained from a proprietary phage library (SK-8 Biotechnologies), selected based on reported activity against *Salmonella* isolates relevant to the Indonesian poultry production. According to the manufacturer, the phages belong to the order *Caudovirales* and include representatives from the families *Siphoviridae*, *Autosignataviridae* (genus *Zindervirus*), and *Andersonviridae* (genus *Felixounavirus*). The phages were selected based on their reported host range and in vitro lytic activity against Salmonella spp., consistent with previous studies demonstrating effective reduction of Salmonella in food and poultry-associated environments (Janania Gamez *et al.*, 2025; Spricigo *et al.*, 2013). However, detailed genomic characterization, including sequence data, accession numbers, and independent confirmation of the absence of lysogenic-associated genes, was not available to the authors.

The VAM-S® bacteriophage cocktail was prepared at two concentrations: $10^9$ PFU/animal (Treatment A) and $10^8$ PFU/animal (Treatment B). Phage concentrations were expressed as plaque-forming units (PFU)/mL as provided by the manufacturer (SK-8 Biotech). Phage was administered orally following *Salmonella* challenge using either weekly or daily dosing regimens. The initial dose was given 48 hours post-challenge, followed by subsequent administrations according to the experimental design Table 1. Two control groups were included: a negative control (challenged, untreated) and a normal control (unchallenged, untreated).

**Table 1:** Experimental groups and dosing regimens for the field trial.

| Group | Treatment | Dose (PFU/animal) | Administration schedule | n |
|---|---|---|---|---|
| G1 | Treatment A (Weekly) | $10^9$ | First dose at 48 h post-challenge (Day 2), followed by doses at 7-day intervals (Days 9 and 16 post-infection) | 10 |
| G2 | Treatment A (Daily) | $10^9$ | First dose at 48 h post-challenge (Day 2), followed by daily dosing for 7 consecutive days (Days 3-9 post-infection) | 10 |
| G3 | Treatment B (Weekly) | $10^8$ | First dose at 48 h post-challenge (Day 2), followed by doses at 7-day intervals (Days 9 and 16 post-infection) | 10 |
| G4 | Treatment B (Daily) | $10^8$ | First dose at 48 h post-challenge (Day 2), followed by daily dosing for 7 consecutive days (Days 3-9 post-infection) | 10 |
| G5 | Negative Control | — | Challenged at 4 weeks of age, no treatment | 10 |
| G6 | Normal Control | — | No challenge, no treatment | 10 |

* Day 0 represents the day of Salmonella challenge. Daily dosing was administered for 7 consecutive days (Days 3–9 post-infection), while weekly dosing was administered on Days 2, 9, and 16 post-infection. The total number of administrations differed between regimens (daily: 8 doses; weekly: 3 doses); therefore, comparisons reflect both dosing frequency and cumulative exposure.

### Clinical monitoring and growth performance

Birds were monitored daily for clinical signs of salmonellosis using a standardized scoring system, including activity, faecal consistency, comb and wattle condition, feather quality, and cloacal cleanliness (Table 2). Mortality was recorded separately. For analysis, clinical scores were summarized as the proportion of affected birds (score ≥1) at each time point to provide a consistent and interpretable outcome across groups. Clinical scoring was conducted by trained personnel using predefined criteria (Table 2). No formal validation or inter-observer reliability assessment was performed; therefore, the scoring system should be considered semi-quantitative and descriptive in nature. Body weight was measured weekly to assess growth performance.

### Microbiological sampling and quantification

### Cloacal swabs

Cloacal swabs were collected at baseline (Day 0), and at multiple time points post-infection (Days 3, 5, 7, 14, and 28) to assess *Salmonella* shedding. Samples were cultured on Xylose Lysine Deoxycholate (XLD) agar.

### Fecal culture

In addition to quantitative cloacal swab analysis, qualitative bacteriological assessment was performed using selected cloacal or fecal samples collected at key time points (Days 0, 3, and 7 post-infection). Samples were cultured on XLD agar, and representative plates were documented to illustrate general trends in Salmonella shedding across experimental groups.

### Ileum content

At the end of the study (Day 28 post-infection), birds were humanely euthanized by electrical stunning followed by exsanguination, performed by trained personnel in accordance with established animal welfare guidelines, including the American Veterinary Medical Association (AVMA) Guidelines for the Euthanasia of Animals. Ileum contents were aseptically collected, homogenized, serially diluted, and cultured on XLD agar for quantification of *Salmonella* load.

### Bacterial enumeration and identification

For both cloacal swab and ileum content cultures, colonies exhibiting typical Salmonella-like morphology (red colonies with or without black centers) were enumerated. Counts were expressed as CFU/mL for cloacal swabs and CFU/g for ileum content. No additional confirmatory identification (e.g., biochemical, serological, or molecular testing) was performed; therefore, results are reported as presumptive Salmonella counts.

### Histopathological examination

Tissue samples from the ileum, cecum, liver, and spleen were collected at necropsy and fixed in 10% neutral-buffered formalin. The samples were subsequently processed, embedded in paraffin, sectioned, and stained with haematoxylin and eosin (H andE) for microscopic evaluation. Histopathological assessment focused on key indicators of tissue integrity and inflammation, including inflammatory cell infiltration, mucosal oedema, epithelial integrity, villus structure and length, and crypt architecture. The evaluation was conducted by a veterinary pathologist from the School of Veterinary Medicine and Biomedical Sciences, IPB University, based on qualitative assessment of representative tissue sections. No formal blinded or semi-quantitative scoring system was applied, and therefore histological findings are presented descriptively. As a result, the histopathological observations should be interpreted with caution, as the absence of blinding and quantitative scoring may introduce subjectivity and potential observer bias.

**Table 2:** Clinical sign parameter scoring criteria used for daily monitoring.

| Parameter | Score 0 (Normal) | Score 1 (Mild) | Score 2 (Moderate) | Score 3 (Severe) |
|---|---|---|---|---|
| Activity and Posture | Active, quick response, normal posture | Slightly lethargic, mildly fluffed feathers | Lethargic, more stationary, obviousfeather fluffing | Refuses to move, hunched or lying down posture |
| Feces (Consistency and-Color) | Solid, normal color | Slightly soft; color unchanged | Diarrhea; greenish- yellow/mucoid | Watery diarrhea; dark green/bloody/strong foul odor |
| Comb and Wattles (Color/Edema) | Bright red, no swelling | Slightly pale or dull red | Pale/mild cyanosis, slight edema | Clear cyanosis/severe edema |
| Feather Quality | Neat, glossy | Slightly dull | Dull & fluffed | Obvious feather loss/fecal-soiled patches |
| Cloaca/Soiling | Clean | Slightly soiled | Moderately soiled (obvious soiling) | Heavily soiled; irritation present |
| Mortality (recorded separately) | - | - | - | - |

### Organ index assessment

Liver and spleen were excised and weighed. Organ indices were calculated as the ratio of organ weight to body weight and expressed as a percentage.

### Statistical analysis

All statistical analyses were performed using R software (RStudio version 2025.09.1+401). Cloacal *Salmonella* counts were analyzed using a linear mixed-effects model to account for repeated measurements within individual birds. Treatment group (Dose), time (Day), and their interaction were included as fixed effects, and bird ID was included as a random effect to account for within-subject correlation. Bacterial counts were $\log_{10}$-transformed prior to analysis to improve normality and homogeneity of variance. Post hoc pairwise comparisons were conducted using Tukey-adjusted tests. Body weight data were analyzed using one-way analysis of variance (ANOVA) at each time point, with Tukey's post hoc test applied for multiple comparisons. Ileum bacterial load and organ indices were analyzed using the non-parametric Kruskal–Wallis test, followed by Dunn's post hoc test with Holm-adjusted p-values to account for multiple comparisons. Histopathological findings were analyzed descriptively. Data were expressed as mean ± standard deviation (SD) or median (interquartile range), as appropriate. Statistically significance was set at $p < 0.05$. Multiple comparisons were controlled within each outcome using appropriate post hoc adjustments (e.g., Tukey or Holm). No global correction across different study endpoints was applied; therefore, results should be interpreted with consideration of potential type I error inflation across endpoints.

### Ethical approval

All experimental procedures involving animals were conducted in accordance with institutional and national guidelines for the care and use of laboratory animals. The study protocol was reviewed and approved by the Animal Ethics Committee of the School of Veterinary Medicine and Biomedical Sciences, IPB University (Bogor, Indonesia), under approval number 407/KEH/SKE/**XI/2025**, issued on 25 November 2025.

## RESULTS

### Clinical symptom score

Clinical monitoring over the four-week post-infection period showed generally similar trends in symptom resolution across groups, with gradual improvement over time. The Normal Control group remained asymptomatic throughout the study. In the Negative Control group clinical signs were observed during the post-infection period, with 3/10 birds affected at Weeks 3 and 4 post-infection and 2/10 birds (20%) still showing clinical signs at Week 5. Bacteriophage-treated groups showed a trend toward lower proportions of affected birds at later time points, particularly in the high-dose groups ($10^9$ PFU/animal), where no birds exhibited clinical signs by Week 5. In contrast, the low-dose weekly group ($10^8$ PFU/animal) retained 1/10 affected birds (10%) at Week 5, while the daily low-dose group showed complete resolution. Overall, these observations suggest a trend toward earlier or more consistent resolution of clinical signs in bacteriophage-treated groups; however, differences in final recovery between treated and untreated groups were modest. As clinical assessments were based on a semi-quantitative scoring system, these findings should be interpreted as descriptive trends rather than precise quantitative comparisons. These observations should be considered alongside growth performance outcomes, as differences in body weight gain were observed between treated and untreated groups.

### Body weight observation

The Negative Control group exhibited the lowest weight gain throughout the study, indicating the detrimental effect of *Salmonella* infection on growth performance. In contrast, all bacteriophage-treated groups (Daily $10^9$, Daily $10^8$, Weekly $10^9$, and Weekly $10^8$ PFU/animal) demonstrated improved growth trajectories, approaching those of the Normal Control group (Figure 1). One-way ANOVA revealed significant differences in body weight among groups ($p < 0.001$). Post hoc Tukey's test indicated that all bacteriophage-treated groups had significantly higher body weights compared to the Negative Control group ($p < 0.05$), while no significant differences were observed between treated groups. These findings indicate that bacteriophage treatment mitigated the negative

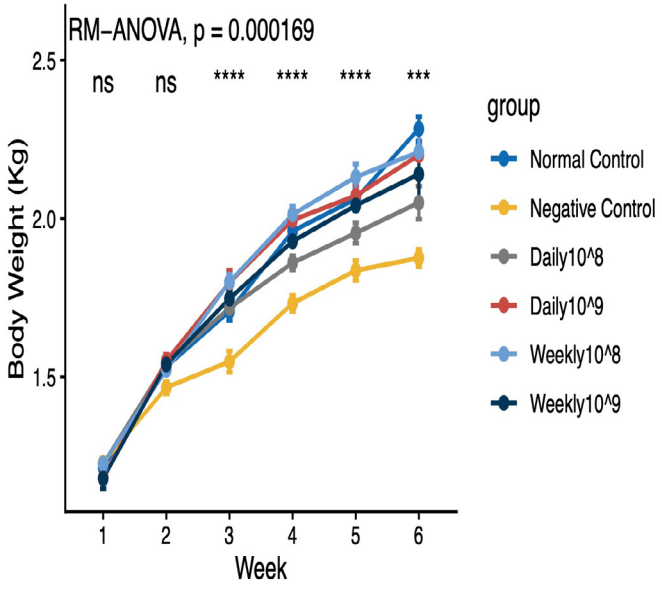


**Figure 1:** Growth performance of broiler chickens following salmonella challenge and bacteriophage treatment_revised.

impact of *Salmonella* infection on growth performance. Both dosing levels and administration frequencies were similarly effective in maintaining growth comparable to uninfected controls, supporting the safety and efficacy of bacteriophage therapy as an alternative strategy for controlling *Salmonella* infection in poultry.

## Faecal culture

Fecal cultures on selective media provided a qualitative visualization of differences in *Salmonella* shedding among experimental groups (Figure 2). Representative plates were selected to reflect the overall trend observed across birds within each group. At 0 days post-infection (DPI), all groups showed minimal or no detectable *Salmonella*, confirming baseline conditions prior to challenge. By 3 DPI, the Negative Control group exhibited a marked increase in bacterial load, characterized by near-confluent growth, confirming successful establishment of infection following challenge. In contrast, all bacteriophage-treated groups ($10^8$ and $10^9$ PFU/animal) showed visibly lower colony densities, indicating an early effect of phage treatment on bacterial shedding. At 7 DPI, the Negative Control group maintained a high bacterial burden, whereas phage-treated groups showed reduced colony density. The Normal Control group remained free of *Salmonella* colonies throughout the study, confirming the absence of contamination. These qualitative observations are consistent with the trends observed in quantitative cloacal swab analysis (Figure 3), particularly during the early post-infection period.

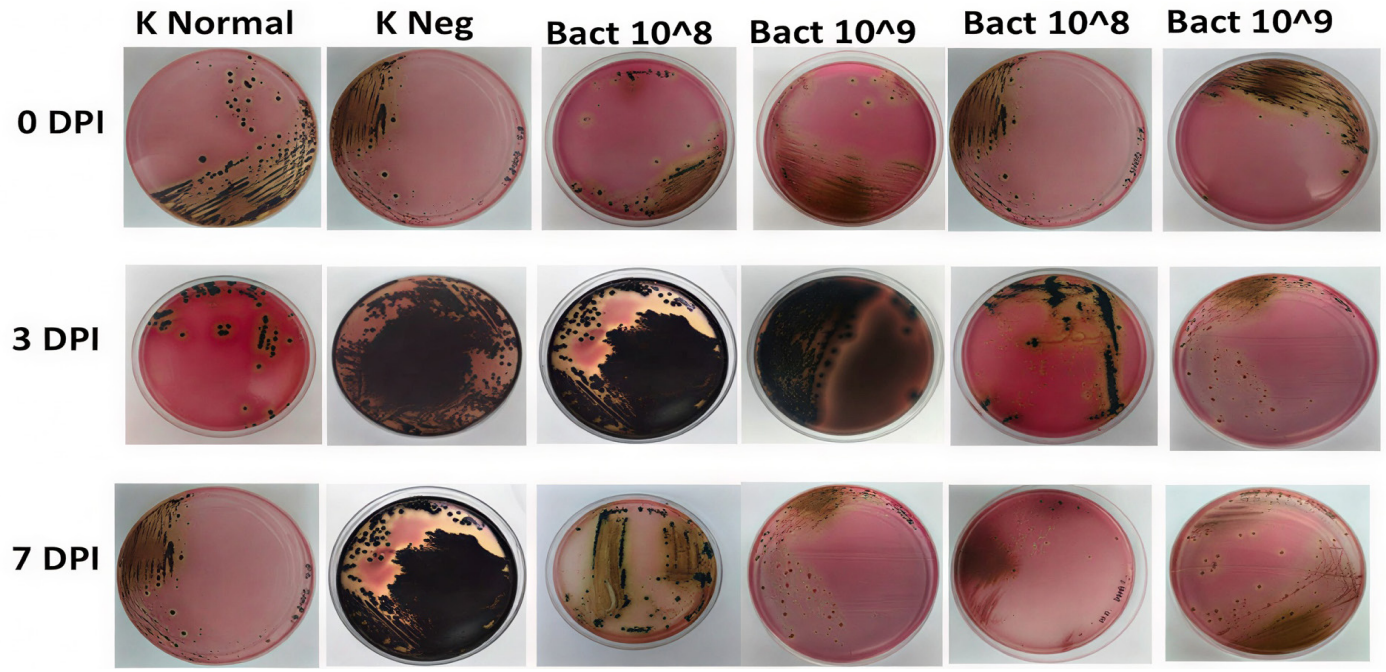


**Figure 2:** Representative fecal culture plates illustrating qualitative differences in Salmonella colony growth across treatment groups at 0, 3, and 7 days post-infection.

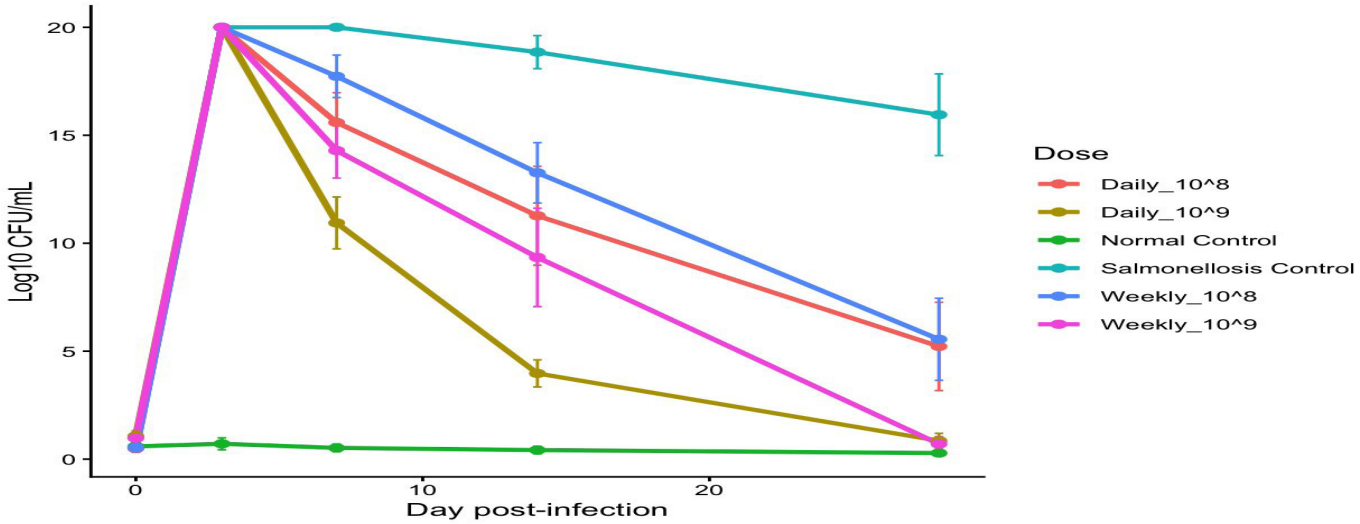


**Figure 3:** Effect of bacteriophage treatment on cloacal salmonella shedding over time_revised_r2.

### Cloacal swab culture

Quantitative analysis of presumptive *Salmonella* concentrations from cloacal swab samples over the 28-day period was performed using a linear mixed-effects model to account for repeated measurements within individual birds. The analysis revealed significant effects of treatment group (Dose), time (Day), and a significant Dose × Day interaction ($p < 0.001$ for all; Figure 3), indicating that changes in bacterial shedding over time differed between groups. At baseline (Day 0), all groups exhibited low bacterial counts, and post hoc comparisons showed no significant differences between groups. Following challenge, all infected groups demonstrated a marked increase in bacterial load by Day 3, with significantly higher counts compared to the Normal Control ($p < 0.001$), confirming successful establishment of infection. No differences were observed among infected groups at this time point. From Day 7 onward, bacteriophage-treated groups exhibited a progressive decline in bacterial shedding compared to the untreated Salmonellosis Control group (Figure 3). Post hoc analysis indicated that several treated groups, particularly the $10^9$ PFU regimens, had significantly lower bacterial counts than the untreated group from Day 7 onward ($p < 0.05$). Differences between treated and untreated groups were most pronounced during the early post-treatment period (Days 7–14), reflecting an accelerated reduction in bacterial load associated with bacteriophage administration.

A dose-dependent effect was observed, with the $10^9$ PFU groups generally showing greater reductions compared to the $10^8$ PFU groups at intermediate time points. However, while some pairwise differences between dosing regimens were detected at specific time points, no consistent superiority of daily over weekly administration was observed across the study period. By Day 28, including the untreated control, indicating substantial natural clearance over time. Although treated groups maintained significantly lower bacterial loads compared to the Salmonellosis Control at this time point ($p < 0.001$), the magnitude of differences between groups was reduced relative to earlier time points. Overall, these findings indicate that bacteriophage treatment is associated with a time-dependent and accelerated reduction in Salmonella shedding, particularly during the early phase following treatment initiation, while later-stage declines likely reflect combined effects of treatment and host-mediated clearance.

### Ileum content culture

Quantitative analysis of bacterial load in ileum content revealed significant differences among treatment groups (Kruskal–Wallis test, $p < 0.001$). The Negative Control group exhibited the highest bacterial load (median 5.30 $\log_{10}$ CFU/g; IQR 5.23–5.64). In contrast, bacteriophage-treated groups showed lower median values, with the daily $10^9$ PFU group at 4.30 $\log_{10}$ CFU/g (IQR 0.00–4.73). This corresponds to an approximate reduction of ~1.0 $\log_{10}$ CFU/g relative to the Negative Control. Dunn's post hoc test with Holm-adjusted p-values indicated that treated groups had significantly lower counts than the Negative Control (adjusted $p < 0.05$). However, no statistically significant differences were detected among treatment regimens, including between daily $10^9$ and daily $10^8$ groups. Given the sample size (n = 10 per group), these comparisons may be underpowered. Overall, bacteriophage-treated groups showed a consistent reduction in ileal bacterial load relative to the untreated group, although the magnitude of reduction was modest and should be interpreted with caution. These patterns, including the higher bacterial load in the Negative Control and lower median values in treated groups, are illustrated in Figure 4.

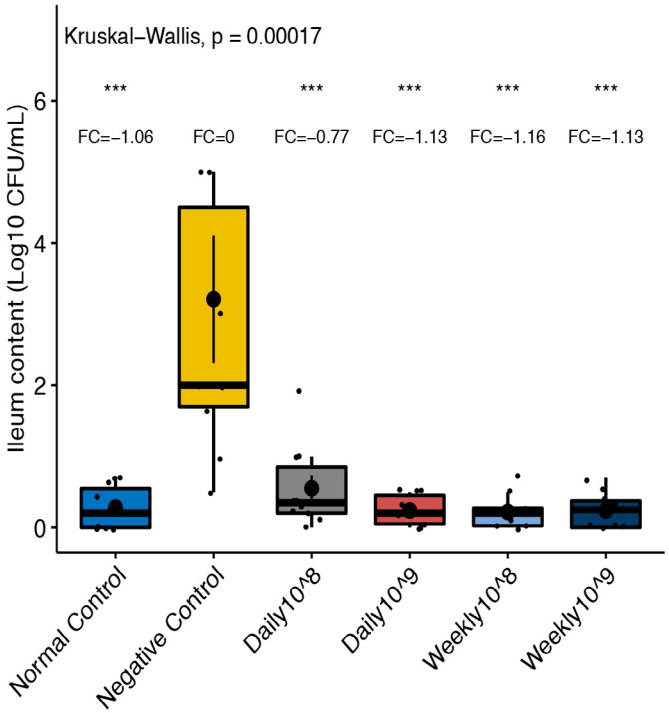


**Figure 4:** Ileal bacterial load across experimental groups at Day 28 post-infection_R2

### Histopathology cecum and ileum

Microscopic evaluation of representative intestinal tissues evealed observable differences among groups. In the cecum, the Negative Control group showed alterations consistent with intestinal inflammation, including disruption of mucosal and crypt architecture and the presence of inflammatory cell infiltration (Figure 5). In contrast, bacteriophage-treated groups ($10^9$ and $10^8$ PFU/animal, administered weekly or daily) appeared to exhibit less pronounced structural alterations, with relatively preserved mucosal and crypt architecture in some sections.

Mild to moderate mononuclear cell infiltration was still observed in certain treated samples. Similarly, in the ileum, the Negative Control group exhibited notable pathological changes, including villus disruption, epithelial damage, and inflammatory cell infiltration (Figure 7). Bacteriophage-treated groups showed partial preservation of villus structure and crypt organization in representative sections, although variability in tissue integrity was observed across treatments. These findings are based on qualitative evaluation of representative tissue sections without blinded analysis or a standardized scoring system and should therefore be interpreted as descriptive observations rather than quantitative evidence of treatment effect.

## Organ index

Analysis of organ indices revealed differences among groups, particularly for the liver index (Figure 7). For the liver index, the Kruskal–Wallis test indicated a significant difference among groups ($p = 0.011$), and post hoc Dunn's test showed that this difference was primarily between the Normal Control and the Negative Control groups ($p < 0.01$). The bacteriophage-treated groups exhibited liver index values comparable to the Negative Control and remained higher than those of the Normal Control. These findings indicates that Salmonella infection was associated with an increase in liver index, and bacteriophage

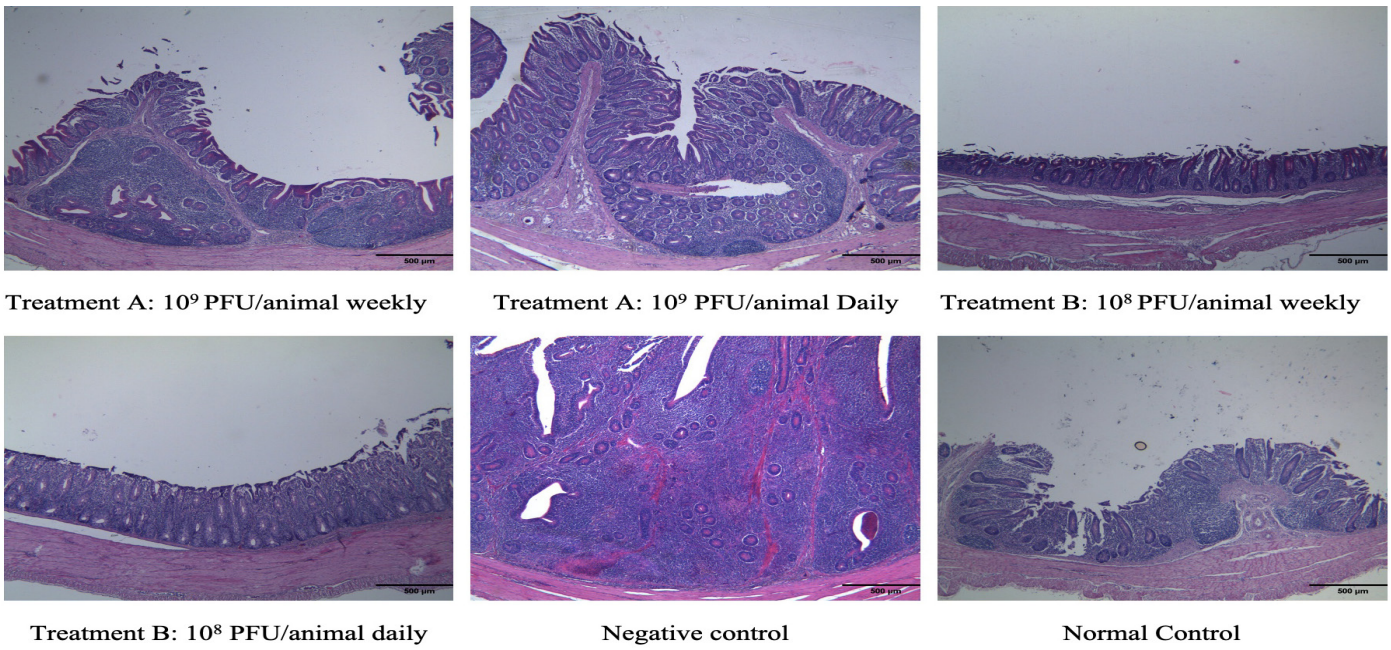


**Figure 5:** Histopathological findings in the cecum (A), and ileum (B) following Salmonella challenge and bacteriophage treatment_revised.

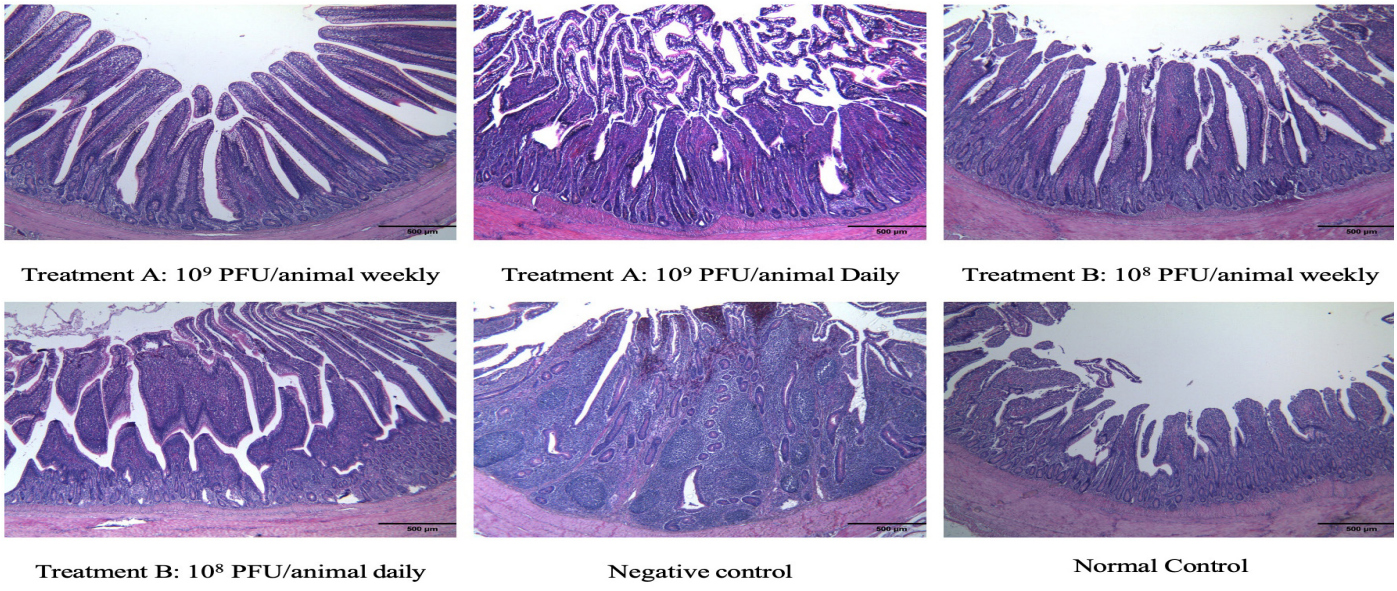


**Figure 6:** Histopathological findings in the cecum (A), and ileum (B) following Salmonella challenge and bacteriophage treatment_revised.

treatment did not restore this parameter to baseline levels within the study period. The persistence of elevated liver index in treated groups should be interpreted with caution, as it may reflect infection-related physiological responses rather than a treatment-specific effect. In contrast, the spleen index did not differ significantly among groups (Kruskal–Wallis, p = 0.42), indicating similar spleen size across treatments and controls.

### Intestinal villi length and integrity

Quantitative measurement of intestinal villi length revealed significant differences among treatment groups (Kruskal–Wallis test, p < 0.001). The Negative Control group exhibited the shortest villi length, consistent with villous atrophy associated with *Salmonella* infection. In contrast, the Normal Control group maintained the longest villi. All bacteriophage-treated groups (weekly and daily administration at $10^8$ and $10^9$ PFU/animal) showed improved villi length compared to the Negative Control. Post hoc Dunn's test indicated that the Negative Control group had significantly reduced villi length compared to the Normal Control and most treatment groups (p < 0.05). Notably, the high-dose weekly ($10^9$ PFU) and daily ($10^8$ PFU) regimens showed villi lengths comparable to the Normal Control group (Figure 8), indicating preservation of intestinal structure following bacteriophage treatment. These quantitative findings are consistent with the histopathological observations (Figure 5), where bacteriophage-treated groups showed partial preservation of villus structure compared to the Negative Control.

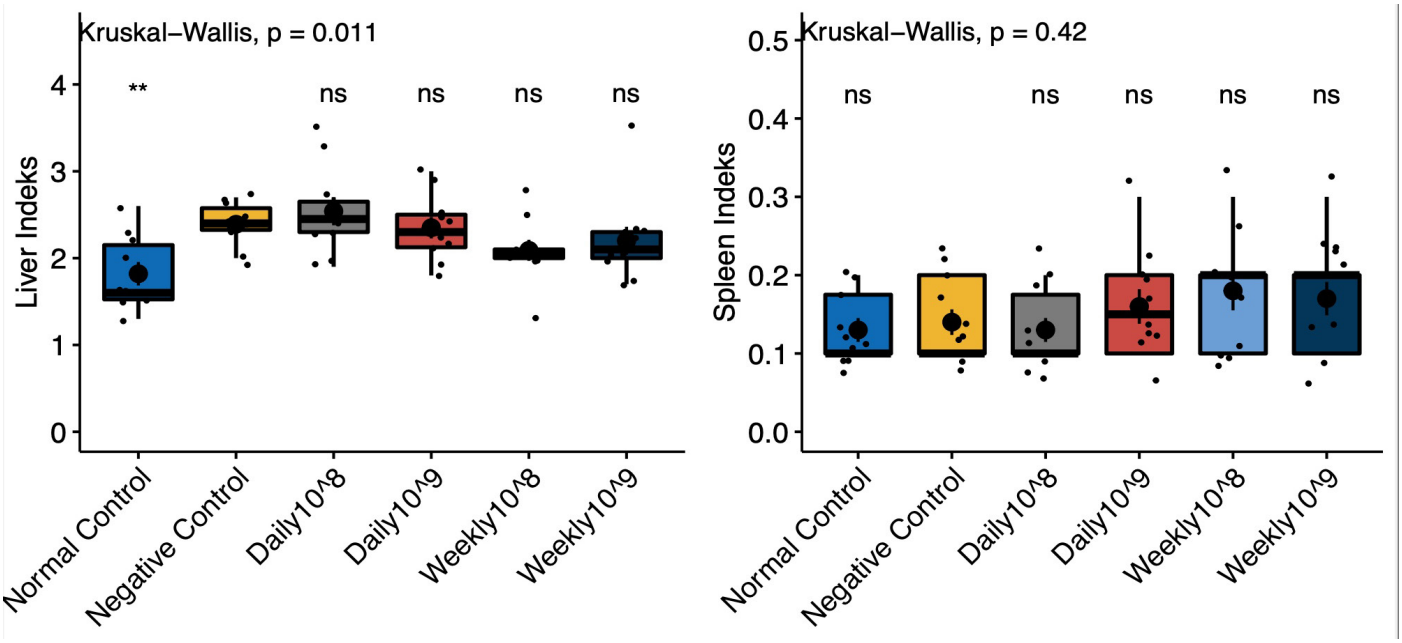


**Figure 7:** Effect of salmonella infection and bacteriophage treatment on liver index and spleen index_revised.

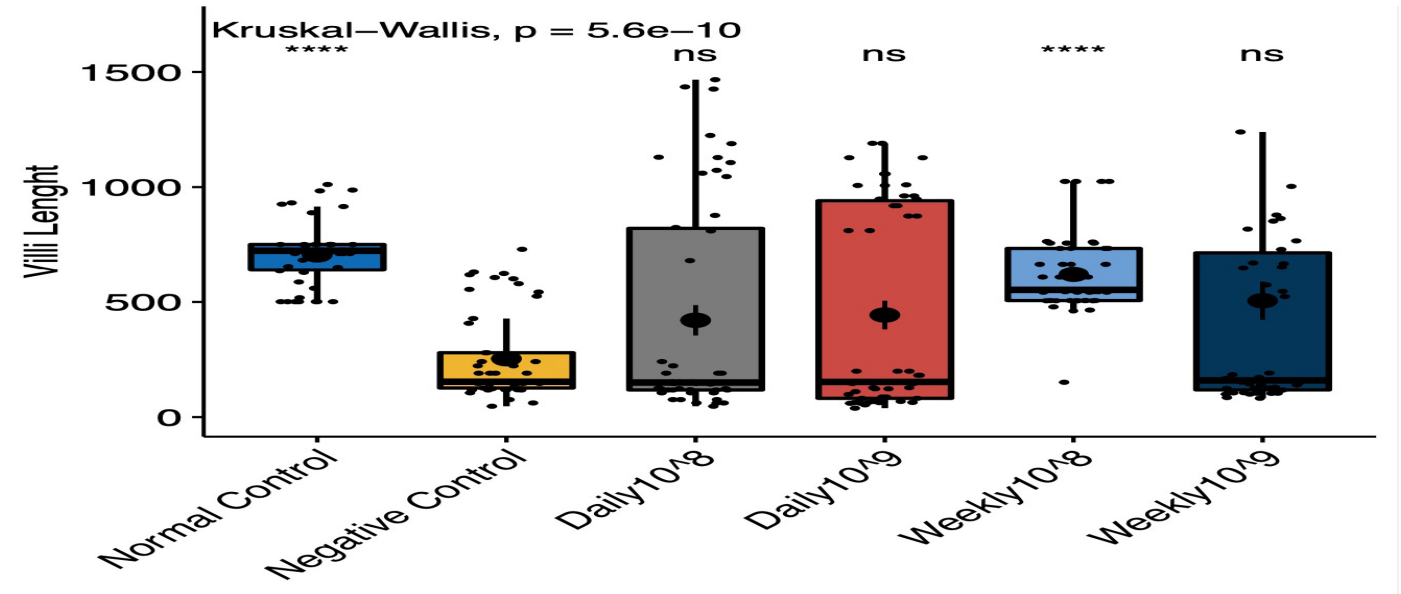


**Figure 8:** Effect of salmonella infection and bacteriophage treatment on intestinal villi length and integrity_revised.

## DISCUSSION

This study demonstrates that oral administration of the VAM-S bacteriophage cocktail reduces Salmonella enterica infection in broiler chickens, as evidenced by decreased bacterial shedding, reduced intestinal colonization, improved clinical outcomes, and preservation of intestinal morphology. These findings support the potential of bacteriophage therapy as an alternative strategy for controlling Salmonella in poultry under controlled experimental conditions relevant to Indonesian poultry productions. The observed reduction in cloacal shedding and ileal bacterial load across treated groups is consistent with previous studies reporting the effectiveness of bacteriophages in reducing Salmonella colonization in poultry (Atterbury *et al*., 2007; Borie *et al*., 2008a; Nabil *et al*., 2024). The progressive decline in bacterial shedding following treatment, particularly in daily dosing regimens, reflects the lytic activity of bacteriophages. This may contribute to enhanced bacterial clearance at the site of the infection (Pelyuntha *et al*., 2022; Wernicki *et al*., 2017). While reductions in bacterial shedding may have implications for limiting environmental contamination and potential transmission within flocks (Abd-El Wahab *et al*., 2023; Żbikowska *et al*., 2020), this study did not directly assess transmission dynamics between birds. Therefore, the impact of bacteriophage treatment on transmission pathways should be interpreted cautiously and warrants further investigation under commercial or flock-level conditions.

In addition to microbiological outcomes, bacteriophage treatment was associated with improved clinical status and growth performance. Although a substantial proportion of birds in the Negative Control group showed clinical recovery by the end of the study, bacteriophage-treated groups generally exhibited earlier and more consistent resolution of clinical signs. Notably, treated birds maintained body weight closer to the Normal Control group, whereas untreated birds showed reduced growth performance despite apparent clinical recovery. This suggests that the benefit of bacteriophage treatment may extend beyond observable clinical signs, contributing to the mitigation of subclinical impacts of *Salmonella* infection that are relevant to production outcomes. These findings are consistent with previous reports demonstrating that bacteriophage supplementation can support growth performance and intestinal health in broiler chickens (Agung Wiono *et al*., 2023; Sarrami *et al*., 2022; Thanki *et al*., 2023).

Similarly, organ index analysis showed that the liver index was elevated in both untreated and bacteriophage-treated infected groups compared to the Normal Control, suggesting that this change is likely associated with Salmonella infection rather than a treatment-specific effect. Infection with Salmonella has been reported to induce hepatic enlargement and inflammatory responses in poultry, reflecting systemic involvement of the pathogen (Barrow, 2007; Wigley, 2024). However, as liver index values did not return to baseline levels in treated groups, this finding warrants cautious interpretation and further investigation. In contrast, the spleen index did not differ significantly among groups, although variability was relatively high. Therefore, the absence of statistically significant differences should be interpreted with caution, as the sample size (n = 10 per group) may limit the ability to detect subtle effects. Overall, these findings do not provide clear evidence of phage-specific adverse effects on organ indices under the conditions of this study. However, given the persistence of elevated liver index in infected groups, these results should be interpreted with caution and warrant further investigation. This is broadly consistent with previous studies reporting the general safety of bacteriophage application in poultry (Kim *et al*., 2013; Ngu *et al*., 2022).

The histopathological findings indicate that bacteriophage-treated birds exhibited improved intestinal morphology compared to the Negative Control, with partial preservation of villus structure and mucosal integrity-features critical for nutrient absorption and immune barrier function. These qualitative observations are supported by the quantitative villus length measurements (Figure 8), which showed higher villus length in treated groups relative to the Negative Control, indicating consistency between structural and morphometric outcomes. These observations are consistent with previous studies suggesting that phage therapy can reduce intestinal damage by lowering bacterial burden and associated inflammation (Muneeb *et al*., 2025; Nabil *et al*., 2024; Sarrami *et al*., 2022). However, this effect varied among treatment groups, and complete restoration to Normal Control levels was not consistently observed. Collectively, these results supports the role of bacteriophages as targeted antimicrobial agents that may contribute to improved gut condition without observable adverse effects on host health under the conditions of this study.

While these findings support the beneficial effects of bacteriophage treatment, several aspects of safety were not directly assessed in this study. Although no adverse effects on growth performance or organ indices were observed, the safety evaluation was limited to clinical and physiological parameters. In particular, this study did not assess potential endotoxin release associated with bacterial lysis or host immune responses following bacteriophage administration. Previous studies suggest that phage-mediated bacterial lysis is generally well tolerated in vivo and does not result

in clinically significant endotoxin-related effects under controlled conditions (Liu *et al*., 2021; Reindel and Fiore, 2017). Additionally, the emergence of phage-resistant Salmonella was not evaluated. Although multi-phage cocktails are designed to reduce resistance development, monitoring resistance dynamics remains important. Future studies incorporating microbiological and molecular analyses are needed to better understand these aspects and support the sustainable use of bacteriophage therapy.

A notable contribution of this study lies in its evaluation of optimal dosing strategies for phage application under controlled conditions relevant to Indonesian poultry productions. Both high-dose ($10^9$ PFU) and moderate-dose ($10^8$ PFU) regimens were associated with reductions in *Salmonella* burden, with the high-dose treatments showing faster improvement in clinical signs and more consistent reductions in cloacal shedding and ileal bacterial load. Daily administration resulted in greater bacterial reduction compared to weekly dosing schedules, indicating that more frequent phage application may improve treatment efficacy. These findings are consistent with previous studies reporting enhanced outcomes with higher phage titres and repeated dosing (Abd-El Wahab *et al*., 2023; Korzeniowski *et al*., 2022; Wernicki *et al*., 2017). However, it is important to note that the daily regimen in this study was applied only for a limited 7-day period during the final production week, rather than throughout the entire rearing cycle. While this short-term intensive dosing strategy may be biologically effective, its practical implementation in large-scale commercial systems requires further consideration. In commercial settings, delivery via drinking water or feed may offer more feasible approaches for administering bacteriophages at scale, as these routes allow flock-level treatment and have been widely used in poultry studies to reduce bacterial colonization and shedding (Abd-El Wahab *et al*., 2023; Borie *et al*., 2008b).

The implications of this study are particularly relevant to Salmonella control efforts in Indonesia, where poultry products remain a recognized reservoir for foodborne pathogens and where high farm- and market-level contamination continues to impede export competitiveness. For example, surveys in Indonesian markets have repeatedly documented high prevalence of *Salmonella* spp. in broiler meat, nearly 48 % in a study from Surabaya markets (Wardhana *et al*., 2021) and up to 75 % contamination in other assessments (Nissa *et al*., 2023), underscoring persistent safety gaps in the poultry value chain. The growing prevalence of antimicrobial resistance (AMR) further limits the efficacy of conventional antibiotic-based interventions; multidrug-resistant *Salmonella* strains from retail chicken meat have been reported in Indonesia (Fanissa *et al*., 2022). This context underscores the urgent need for scalable, residue-free antimicrobial solutions within the national poultry sector.

Bacteriophage therapy satisfies this requirement by providing pathogen-specific control without necessarily contributing to AMR selection pressures and without leaving chemical residues that could trigger border rejections or violate international trade standards. Indeed, recent studies demonstrate successful phage-based reductions of *Salmonella* in poultry products and live birds (Hungaro *et al*., 2013; Kuźmińska-Bajor *et al*., 2023). The demonstrated safety, efficacy, and dose responsiveness of the VAM-S phage cocktail in the present study highlight its potential to serve as a promising component in integrated *Salmonella* management programs. By reducing bacterial load in flocks and improving health without antibiotic residues, phage therapy supports Indonesia's strategic objective of expanding poultry exports while safeguarding public health and meeting global biosecurity requirements.

This study has several limitations. First, the Salmonella enterica isolate was not fully characterized at the serovar level, and neither antimicrobial resistance profiling nor phage susceptibility testing was performed, which may limit the generalizability of the findings. In addition, the absence of a distinguishable marker limits the ability to definitively differentiate the challenge strain from potential environmental Salmonella, although baseline screening confirmed birds were negative prior to challenge. Second, the experimental design was conducted under controlled conditions does not fully reflect commercial farm environments, where birds face continuous infection pressure and variable management practices. The relatively small sample size (n = 10 per group) may also limit statistical power. In addition, given the number of outcomes assessed, there is a potential for type I error inflation across endpoints; therefore, findings should be interpreted in the context of consistency across results and biological plausibility.

Third, microbiological enumeration was based on colony morphology on XLD agar without confirmatory identification. As XLD agar is not fully selective, some colonies may represent non-Salmonella Enterobacteriaceae; therefore, results should be interpreted as presumptive Salmonella counts. Fourth, both histopathological assessment and clinical scoring were based on qualitative or semi-quantitative approaches without blinded analysis, standardized scoring validation, or inter-rater reliability assessment, which may introduce subjectivity and potential observer bias in outcome evaluation. Fifth, the study did not include a phage-only control or a non-susceptible bacterial strain, limiting the ability to distinguish the relative contribution of bacteriophage activity from natural host-

mediated clearance. Additionally, phage concentrations were based on manufacturer-provided value without independent verification, and in vivo phage dynamics were not evaluated. Therefore, it remains unclear whether the observed effects were driven by phage replication, sustained activity, or repeated dosing.

Despite these limitations, the most robust finding of this study is the consistent directional reduction in bacterial burden in bacteriophage-treated groups compared to the Negative Control, observed across multiple independent endpoints (cloacal shedding, ileal bacterial load, and growth performance). The convergence of these outcomes provides supportive evidence of a biologically relevant effect, even though the magnitude of reduction was modest and should be interpreted cautiously. Future studies under commercial conditions, incorporating larger sample sizes, strain characterization, blinded histopathological scoring, confirmatory microbiological methods, and longitudinal statistical models, are needed to validate these findings and assess the practical applicability of bacteriophage therapy in poultry production systems.

## CONCLUSION

This study indicates that the VAM-S bacteriophage cocktail were associated with reductions in *Salmonella enterica* shedding and intestinal colonization in broiler chickens under controlled experimental conditions. These effects were accompanied by trends toward improved clinical outcomes and partial preservation of intestinal morphology, although complete restoration to Normal Control levels was not consistently observed. While bacteriophage-treated groups showed no clear evidence of adverse effects on growth performance or tissue integrity, liver index remained elevated in both treated and untreated infected groups, indicating that infection-related physiological changes were not fully resolved and warrant further investigation. Importantly, this study was conducted at a small scale under controlled conditions, and its findings should not be directly extrapolated to poultry systems. Practical implementation, including delivery methods (e.g., via drinking water or feed), cost-effectiveness, dosing logistics, and the potential emergence of phage-resistant bacterial populations were not assessed. Therefore, bacteriophage therapy should be considered a complementary approach, rather than a replacement for established control measures such as biosecurity, hygiene, and vaccination. Overall, these findings support the potential of bacteriophage therapy as a targeted and residue-free antimicrobial approach for reducing Salmonella infection and contributing to antimicrobial resistance mitigation. Further studies under commercial production conditions are needed to evaluate its operational feasibility and to validate its role within integrated, sustainable poultry health and food safety strategies in Indonesia.

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## NOVELTY STATEMENT

The novelty of this study is the evaluation of the VAM-S bacteriophage cocktail in broiler chickens challenged with *Salmonella enterica* using dose- and frequency-based treatment regimens relevant to Indonesian poultry production, with assessment of bacterial shedding, ileal colonization, clinical response, and intestinal histopathology.

## AUTHOR CONTRIBUTION

HY, JN, MS: Idea and research design. HY, MS, and ET: Field Trial, Data collection, sample collection, laboratory analysis. KT and OP: Funding. HY and MS: Write the manuscript. HY: Revision

### Generative AI and AI assisted technology statement

The authors declare that no generative AI and AI assisted technology was used in the creation of this manuscript.

### Conflict of interest

The authors declare that this study received financial and material support from SK8 Biotechnologies Inc., Canada. Authors affiliated with SK8 Biotechnologies Inc., were involved in study design and funding but had no role in data collection and analysis. All authors declare that the results are presented objectively without undue influence.

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