

Bacteriophages as Prophylactic Agents Against Gram-Negative Pathogens in Poultry Production

AUTHORS DETAIL

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Abstract

The rising threat to the global food supply of antimicrobial resistance (AMR) in the poultry-related pathogens, especially Gram-negative *Salmonella spp.*, *Escherichia coli*, and *Campylobacter jejuni*, has triggered the pursuit of suitable, non-antibiotic alternatives to address such infections. One of these promising solutions is the bacteriophage therapy, a natural process whereby the bacteriophages, viruses that specifically attack and lyse the bacteria, provide an environmentally friendly, targeted method of control of pathogens. With the problem of prevalence of AMR in poultry farming persisting to increase over time, bacteriophages make a strong case as an alternative to established antibiotics. The chapter also explores the application of bacteriophages as prophylactic agents, their biological characteristics, and mechanisms of action (i.e. bacterial lysis, biofilm disruption, quorum sensing interference), and their application routes such as oral delivery, feed and water additives, and spraying of the environment. Also, it discusses their use in multidrug-resistant (MDR) pathogen targeting, their safety profile and the regulatory implications of their use. The benefits of phage therapy such as high host specificity, low effects on the beneficial gut microbiota, and the absence of any chemical residue in poultry products. Difficulties facing phage use such as phage-host specificity, bacterial resistance and regulatory barriers are addressed. In addition, the chapter discusses the latest advances in the area of phage therapy, including genetically modified phages and CRISPR-Cas9 technologies, which may address the existing limitations. Eventually, phage therapy can potentially form an important part in combating AMR in chickens, which will lead to more sustainable and antibiotic-free agriculture.

Keywords: Poultry health, antimicrobial resistance (AMR), phage therapy, alternative to antibiotics, bacteriophage, multidrug-resistant pathogens.

Introduction

Poultry farming is one of the pillars of food production in the world as it is one of the primary sources of meat and eggs everywhere. Nevertheless, it is quite problematic because of the presence of Gram-negative bacterial pathogens that pose threats to the health of poultry and food safety (Zhang et al., 2022). Interestingly, *Salmonella spp.*, *Escherichia coli*, *Campylobacter jejuni*, and *Pseudomonas aeruginosa* are the most likely bacterial risks in poultry systems, which cause diseases that vary between enteritis and septicemia to chronic infections (Abreu et al., 2023). Transmission of these pathogens through contaminated poultry products increases the public health risk posed by the pathogens, causing human foodborne diseases (Dam and Chakraborty, 2025).

In the past, antibiotics have been highly applied in rearing poultry, in treatment, as well as growth promoters. Nevertheless, the excessive application and misuse of antibiotics have led to the development of antimicrobial resistance (AMR) which has a severe impact on the health of animals, food security as well as human health (Huang et al., 2022). Many countries have come

up with regulations to reduce the use of antibiotics in food animal production as a response to the escalating concerns about AMR (Makumi et al., 2021). This has seen researchers consider other sustainable ways of curbing bacterial infections among poultry with bacteriophage therapy being a promising solution (Sharma et al., 2025).

Phages (also known as bacteriophages) are viruses that can specifically lyse bacterial cells and provide a specific method of using viruses as a means of controlling pathogens (Guantai, 2022). Phages can be considered as a potential substitute to traditional antibiotics because of their distinct characteristics such as high host specificity and capability to replicate at an infection site (Bianchessi et al., 2024). Moreover, phages do not interfere with the normal microbiota like antibiotics, and thus are a promising option of keeping the gut microbiome balanced in poultry (Li et al., 2022).

This chapter is a review of the existing status of bacteriophages study and its use in chickens farming. It is about the biological properties of phages, their mode of action, administration route, challenges and opportunities of using phages. It also gives an idea about the recent developments in phage therapy including engineered phages and the application of phage-derived enzymes that can potentially overcome the current shortcomings and enhance the effectiveness of the phage-based therapies.

Major Gram-Negative Pathogens in Poultry

1. *Salmonella* spp.

Salmonella is a major poultry pathogen where *Salmonella Enteritidis* and *Salmonella Typhimurium* are the most frequently isolated serovars. These bacteria are known to produce paratyphoid infections that result in diarrhea, septicemia and most of the time death in birds (Li et al., 2022). Birds that are infected release the bacteria in feces, which contaminate meat and eggs, which are the major sources of infection in humans. *Salmonella* infections have become a significant issue to the health of the people because they are zoonotic, and thus, they cause millions of foodborne diseases worldwide (Zhang et al 2024).

Recently, there has been a report of multidrug-resistant (MDR) *Salmonella* strains, which are resistant to ceftriaxone, ciprofloxacin and other antibiotics, in poultry. This resistance makes it difficult to plan treatment and it is very likely that resistant bacteria may be transferred to people (Jung et al., 2023). Bacteriophage therapy is an excellent alternative to conventional antibiotics in the management of *Salmonella* infection in poultry as research shows that colonization and shedding in broilers can be reduced with the application of phages (Sun et al., 2024).

2. Avian Pathogenic *E. coli* (APEC)

One of the leading causes of colibacillosis in poultry are avian pathogenic *Escherichia coli* (APEC), which results in massive losses to the poultry industry. Strains of APEC with serotypes O1, O2 and O78 can lead to serious infections, airsacculitis, peritonitis and septicemia. The diseases have high death rates and low productivity especially to the young chicks and layer hens (Mehat et al., 2021). The MDR strains of *E. coli* emerging in poultry production have further complicated treatment due to the fact that most of them are resistant to the most commonly used antibiotics like fluoroquinolones and tetracyclines (Joseph et al., 2023). Phage therapy has been found to be a promising treatment of APEC infections, and experimental studies have found that phages can lower mortality and enhance the health of flocks (Runcharoon et al., 2025). Moreover, the phage treatment in hatcheries has been successful in averting the premature chick death and this suggests the potential of phage-based interventions in the key stages of poultry growth (Hu et al., 2022).

3. *Campylobacter jejuni*

One of the significant food-borne gastroenteritis causes is *Campylobacter jejuni*, which is mostly linked to the consumption of undercooked poultry meat. *C. jejuni* frequently causes a silent colonization of the intestinal tract in poultry, thereby making it challenging to eliminate and causing no overt symptoms (Al Hakeem et al., 2022). The organism is very resistant and can survive in the intestinal environment of chickens, and can also survive in the poultry processing environment, which also increases the risk of contamination (Rzeznitzeck et al., 2022).

Management of *C. jejuni* in poultry farms has been difficult because it can colonize without any symptoms. Nevertheless, recent research has demonstrated that the *C. jejuni* bacteriophage can be used to decrease intestinal colonization of chickens and also reduce the bacterial load within processing plants (Hur et al., 2024). The use of phages in pre-slaughter stage has proved specifically useful in eliminating contamination hence minimizing the possibility of human contamination (Amjad, 2023).

4. *Pseudomonas aeruginosa*

P. aeruginosa is an opportunistic pathogen which leads to chronic infections in poultry and specifically in the respiratory and intestinal tract. The organism is known to establish biofilms whereby it safeguards the bacteria against antibiotic therapy and immune system reactions (Abd El-Ghany, 2021). This biofilm growth makes it difficult to eliminate *P. aeruginosa* in poultry farms and this survival in the processing environment poses additional issues with regard to contamination (Kumar, 2024).

Phage treatment of *P. aeruginosa* has been found to be effective in the prevention of biofilm formation and the management of chronic poultry infections. Although the current studies on the use of phage therapy against *P. aeruginosa* in poultry are limited, the research shows that the phages are potentially a useful tool in managing the disease, particularly in the poultry processing environment (AMUSAN, 2023). Table 1 gives a summary of prevalent Gram-negative pathogens of the poultry, emphasizing their clinical picture and zoonotic hazard.

Table 1: Major Gram-Negative Pathogens in Poultry and Their Characteristics

Pathogen	Common Species/Serovars	Primary Clinical Manifestations	Zoonotic Risk
<i>Salmonella spp.</i>	<i>S. Enteritidis</i> , <i>S. Typhimurium</i>	Diarrhea, septicemia, reduced productivity	High (meat and eggs)
<i>E. coli (APEC)</i>	O1, O2, O78	Airsacculitis, peritonitis, septicemia	Low (rare human infections)
<i>Campylobacter jejuni</i>	None (species-specific)	Asymptomatic in poultry, but causes gastroenteritis in humans	High (undercooked meat)
<i>Pseudomonas aeruginosa</i>	None (species-specific)	Respiratory and intestinal infections, biofilm formation	Low (opportunistic infections)

Antibiotic Overuse and the Rise of Antimicrobial Resistance

Due to the excessive use of antibiotics in poultry production, the phenomenon of AMR has been identified, and numerous pathogens became sensitive to several categories of antibiotics (Tian et al., 2021). In poultry production, antibiotics are usually administered as a disease-treating method, but they are also applied as growth promoters. It has become so pervasive that it has put selection pressure on bacterial populations, favoring the evolution of resistant organisms (Kariuki et al., 2023).

To address AMR concerns that have been on the rise, governments of most countries have placed prohibitions on the use of antibiotics as growth promoters. Such a ban was introduced by the European Union in 2006, then in the United States in 2017, the Veterinary Feed Directive (Habiba et al., 2023). Nevertheless, AMR continues to pose a great threat in the poultry industry, and alternative methods to control pathogens are much-needed (Panyako et al., 2023).

Phage therapy is another option to antibiotics because phages are very specific to their bacteria and can be used to tackle MDR pathogen. As opposed to antibiotics, phages do not develop resistance to the same effect and can actually be utilized in the treatment of antibiotic-resistant infections (Islam et al., 2024). Furthermore, phages do not affect the healthy microbiota, and thus, it makes them safer and more sustainable in the control of bacterial infections in poultry (Mudenda et al., 2022).

Bacteriophages: Nature's Bacterial Predators

Bacteriophages or phage are bacteria viruses. Phages are very diverse and are present in practically all the environments such as the gut of animals and in the natural habitats of the poultry (Węgrzyn, 2022). Phages bind to bacterial surface and integrate into the host cell. The host cell then turns into a phage factory producing new phage particles which in turn lyse the bacterial cell and release progeny phages which in turn infect other bacteria (Abd-El Wahab et al., 2023).

Phages are very specific on their bacterial hosts and they only attack a few strains or species. This particularity is one of the main benefits in the context of poultry production, where it is possible to selectively destroy pathogenic bacteria without harming the beneficial microbiota of the gastrointestinal tract (Tellez et al., 2024). Also, phages are self-amplifying, which implies that they are capable of multiply where they are introduced into the bacteria population, making them more effective (Atterbury and Tyson, 2021).

Phage therapy is not thought to be very dangerous, since it is biodegradable and phages are naturally occurring. Nonetheless, some problems are related to their application in poultry production including the possibility of bacterial resistance, phage-host specificity and the necessity of adequate storage and application procedures (Thanki et al., 2021).

Mechanisms of Phage Therapy in Poultry

Phage therapy can also be used to treat bacterial infections in poultry in a variety of ways. Bacterial lysis is the main process, in which bacteria are infected by phages, which in turn replicate themselves in the cells and then rupture the cell when they enter the lytic stage of their lifecycle (Zhang et al., 2022). Besides direct bacterial killing, the formation of biofilms which is a frequent occurrence in chronic bacterial infection especially in the poultry processing environment can also be interfered with by the phages (Abbas et al., 2022). Phages have also been found to disrupt the operation of quorum sensing, a bacterial communication process that helps to regulate virulence factors and biofilm formation. Phage treatment may be used in different forms in poultry production (Jiang et al., 2024). The common ways are the oral delivery by feed and drinking water and the

spraying of the environment to control the pathogens in the poultry inside. Furthermore, phages may also be sprayed onto processing equipment in order to minimise contamination of meat in the slaughter and meat processing process (Fig. 01) (Olson et al., 2022).

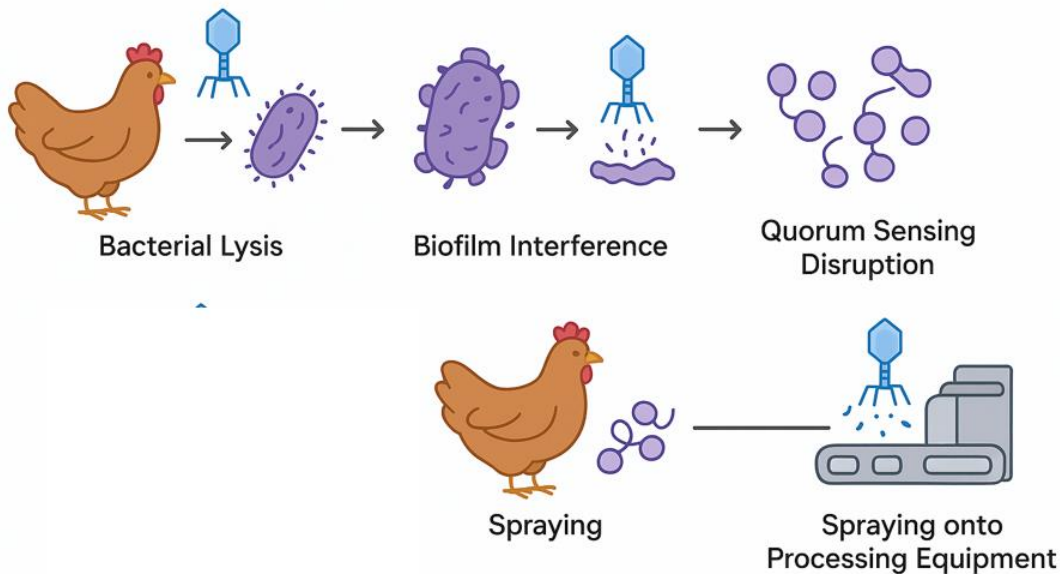


Fig. 01. Mechanisms of phage therapy in poultry, including bacterial lysis, biofilm interference, quorum sensing disruption, and delivery methods (oral, spraying, equipment treatment)

Applications of Phages Against Gram-Negative Poultry Pathogens

1. Phages Against *Salmonella* spp.

Phage therapy also has demonstrated efficacy in reducing the colonization of *Salmonella* in poultry, and several studies have shown that the oral administration of *Salmonella*-specific phages can be used to reduce intestinal colonization and shedding of *Salmonella* (Zagaliotis et al., 2022). Phage cocktails (consisting of multiple phages of different serovars of *Salmonella*) were discovered to be more effective than single-phage treatment because this strategy minimizes the possibility of bacterial resistance (Jordá et al., 2023).

2. Phages Against APEC

Phage therapy has also been proven to decrease mortality of broilers infected with pathogenic strains in the case of *E. coli*. Research has indicated that the treatment of phage has potential to enhance the wellbeing of infected birds and the level of antibiotic medication in poultry farms dramatically decreases (Eid et al., 2022). Phages have been employed in hatcheries as a means of averting premature death of chicks which has been a valuable instrument in enhancing poultry health at critical stages (Pilati et al., 2023).

3. Phages Against *Campylobacter jejuni*

The colonization of *Campylobacter* in the ceca of the chickens at the pre-slaughter stage can be mitigated by the application of phages leading to the minimization on the risk of contamination in the processing plant. *C. jejuni* phages have been demonstrated to lower bacteriologic loads in poultry resulting in a decline in food-borne disease outbreaks attributed to poorly cooked poultry meat (Tung et al., 2025).

4. Phages Against *Pseudomonas aeruginosa*

Although the investigation on phage therapy as an intervention of *Pseudomonas aeruginosa* in poultry is very young, encouraging outcomes have been witnessed in biofilm management researches (Yilmaz et al., 2025). Phages against *P. aeruginosa* were also found to minimize biofilm formation in poultry and processing plants, and can therefore be useful in managing chronic infections and contamination risks (Mosimann et al., 2021).

Advantages of Phage Prophylaxis

Phage therapy offers several key advantages over traditional antibiotic treatments:

- **Specificity:** Phages are highly specific to their bacterial targets, reducing the impact on beneficial bacteria and minimizing the risk of disrupting the poultry microbiome (Makumi et al., 2021).
- **Self-Amplification:** Phages replicate at infection sites, increasing in number as they infect and kill bacteria, making them highly effective even at low doses (Xu, 2021).
- **Environmental Safety:** Phages are naturally occurring and biodegradable, posing minimal environmental risk (Ge et al., 2022).
- **Efficacy Against MDR Pathogens:** Phages can target and kill antibiotic-resistant bacteria, presenting a possible resolution to the increasing problem of AMR in poultry production (Alomari et al., 2021).

Table 2 indicates that some of the advantages of bacteriophage therapy are its high specificity and absence of residues of the assigned chemical in poultry products, although there are challenges such as development of bacterial resistance, and the barrier of regulatory approval.

Table 2: Advantages and Limitations of Phage Therapy in Poultry Production

Category	Advantages	Limitations	Implications for Poultry
Host Specificity	Highly specific to bacterial targets, minimizing impact on gut microbiota	Requires precise matching to target bacterial strains	Effective against specific pathogens without disrupting commensals
Self-Amplification	Phages replicate at infection sites, enhancing efficacy	Resistance can develop, potentially diminishing long-term effectiveness	May require regular reapplication or new cocktails to maintain efficacy
Efficacy Against MDR	Effective against multi-drug-resistant (MDR) pathogens	Bacteria can still develop resistance to phages, though at a slower rate	Offers a solution to AMR, especially in treatment-resistant strains
Environmental Safety	Biodegradable and naturally occurring, reducing environmental impact	Stability can be influenced by external conditions like temperature or pH	Proper storage and application needed to ensure phage efficacy
No Chemical Residues	No antibiotic residues in meat or eggs, safe for human consumption	May not be as effective on certain pathogens without combination therapy	Crucial for meeting food safety regulations and consumer demand for antibiotic-free products
Targeted Action	Phages target only specific pathogens, reducing collateral damage to the microbiome	May not be effective for all types of pathogens, requiring phage cocktail development	Focused pathogen control minimizes negative impacts on the microbiota
Regulatory Approval	Phages are natural, with a long history of safety	Regulatory approval pathways are still under development in many countries	Potential regulatory hurdles before widespread adoption in the poultry industry
Production and Cost	Phage production is relatively low-cost and scalable	Large-scale production and cost-efficiency need further optimization	Economically viable alternative to antibiotics, but needs to be scalable for mass poultry farming

Limitations and Challenges

Despite their advantages, phage therapy faces several challenges:

- **Bacterial Resistance:** Bacteria can develop resistance to phages, although this process is generally slower than resistance to antibiotics (Zagalotitis et al., 2022).
- **Strain Specificity:** Phages are highly specific to particular bacterial strains, meaning that careful selection and matching are required for effective treatment (Jiang et al., 2024).

- **Storage and Stability:** Phages can be sensitive to environmental conditions, and their stability during storage and feed processing needs to be optimized (Zia and Alkheraije, 2023).
- **Regulatory Barriers:** The regulatory approval process for phage-based treatments is still under development in many countries, posing a barrier to widespread adoption in the poultry industry (Ranveer et al., 2024).

Future Perspectives

Overcoming the resistance, strain specificity, and stability challenges faced by phage therapy are the future of phage therapy in poultry production. Current studies are targeting genetically modified phages including those which have been modified with CRISPR-Cas9 technology, which could provide expanded host ranges and better efficacy (Alexyuk et al., 2025). Also, the use of phage therapy combined with other treatment methods, including probiotics or phage-derived enzymes (endolysins), might be used as a synergistic approach to control pathogens (Loponte et al., 2021).

With the implementation of phage therapy as a part of biosecurity, poultry producers will be able to cut down on antibiotic use and curb the ever-increasing AMR threat. The mass production of phages and the optimization of delivery systems will be the key to the popularization of phage-based therapies in the poultry industry (Torres-Boncompte et al., 2025).

Conclusion

Bacteriophage therapy has a potential as an alternative to antibiotics in poultry production, as it is an effective targeted, sustainable method of controlling Gram-negative bacterial pathogens. Phages have been effective in managing *Salmonella*, *E. coli*, *Campylobacter jejuni*, and *Pseudomonas aeruginosa*, and may be important in reducing the risks of AMR. Nevertheless, there are still issues like phage resistance, strain specificity and regulatory obstacles. The further studies of the genetically engineered phages and new strategies of application will be required to get over these restrictions and guarantee the wide implementation of the phage therapy in poultry farming. Phage therapy is a more likely tool of the future of poultry health and food safety as the world poultry industry shifts to more sustainable and antibiotic-free practices.

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