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REVIEW ARTICLE

Innovations in Poultry Disease Control: Advancements in Bacteriophage Therapy and Delivery Systems

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ABSTRACT

Poultry production is a vital source of dietary protein globally, but it faces ongoing challenges from bacterial diseases such as salmonellosis, colibacillosis and necrotic enteritis (NE). These infections not only compromise poultry health but also lead to significant economic losses and pose serious zoonotic risks to human health. Traditionally, antibiotics have been the primary method for controlling these bacterial diseases. However, the overuse and misuse of antibiotics have contributed to the rapid emergence of antimicrobial resistance (AMR), rendering many treatments ineffective and facilitating the spread of resistant bacterial strains. This review explores the urgent need to advance poultry disease management through alternative strategies, with a focus on bacteriophage therapy. Bacteriophages, viruses that selectively infect and destroy bacteria, offer a targeted approach to treating bacterial infections, including those caused by antibiotic-resistant strains. Phage therapy has shown promising results in reducing bacterial loads of pathogens like *Salmonella*, *Campylobacter*, and *Escherichia coli* in poultry, while minimizing negative environmental impacts. Additionally, the review highlights innovative encapsulation and delivery techniques that can enhance phage stability and controlled release in the poultry gut. Bacteriophage therapy shows promise as a solution to antibiotic resistance (AMR) in poultry farming, but it faces ethical and regulatory challenges that need to be resolved. The paper concludes that, with advancements in delivery and encapsulation technologies, bacteriophage therapy offers a sustainable way to reduce antibiotic use, improve poultry health, and ensure the safety of poultry products for human consumption.

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INTRODUCTION

Poultry is a critical component of global food systems, providing a substantial portion of the population with essential protein through meat and eggs (Pius *et al.*, 2021). However, the industry faces significant challenges from bacterial diseases such as salmonellosis, colibacillosis, and other infections, which negatively impact poultry health and productivity. These diseases, caused by bacteria like *Salmonella, campylobacter* and *Escherichia coli*, lead to high morbidity and mortality rates in poultry flocks, resulting in increased veterinary expenses and biosecurity measures (Grace *et al*., 2024).

Salmonellosis, in particular, poses serious concerns due to its zoonotic nature, as infected poultry can transmit the bacteria to humans through contaminated meat and eggs (Gast *et al*., 2024). The economic burden associated with managing salmonellosis is significant, with losses due to decreased productivity, higher mortality rates, and increased disease control measures, amounting to millions of dollars annually (Shaji *et al*., 2023). Similarly, colibacillosis, primarily related to respiratory diseases in poultry, leads to poor feed conversion ratios, low body weight, and elevated mortality, all of which negatively affect the industry's profitability (Serbessa *et al*., 2023). The substantial economic losses coupled with public health concerns underscore the critical need for effective strategies to control and manage these infections.

For decades, antibiotics have been the mainstay of bacterial disease management in poultry. However, the overuse and misuse of antibiotics have led to the emergence of antibiotic-resistant bacteria (AMR), which diminish the efficacy of conventional treatments. AMR has forced the poultry industry to rely on more potent and costly antibiotics, exacerbating production costs and creating an economic strain (Panyako *et al*., 2022). Moreover, antibiotic residues in poultry products pose health risks to consumers, while the environmental pollution caused by antibiotic runoff raises concerns about long-term sustainability (Tian *et al*., 2021). Given the limitations and risks associated with the use of antibiotics, exploring and implementing alternative strategies is vital to ensure continued poultry health and productivity, protect consumer health, and combat the spread of antimicrobial resistance (Abreu *et al*., 2023).

Bacteriophage therapy has emerged as a promising biocontrol strategy. It uses viruses to specifically target and kill bacterial cells without affecting beneficial bacteria in the poultry gut, reducing the likelihood of collateral damage (Harshitha *et al.* 2022; Mills *et al*.,2017). This targeted action makes phage therapy a valuable tool in managing bacterial infections (Zhang *et al*., 2022). Research has demonstrated the efficacy of bacteriophages in controlling pathogens such as *Salmonella spp*, *Campylobacter spp*, and *E. coli* in poultry. For instance, adding phage cocktails to poultry diets has been shown to reduce *Salmonella spp* colonization in the gut, minimizing the risk of transmission through meat products (Siddique *et al. 2018;* Kwaśnicka *et al*., 2022). Similarly, phages specific to *Campylobacter spp,* have reduced bacterial density in broiler chickens, improving overall flock health (Olson *et al*. 2022; Ushanov *et al*., 2020). The application of bacteriophages offers several advantages over conventional antibiotic treatments. They can be administered orally through feed or drinking water, or via sprays in poultry housing environments. Furthermore, bacteriophages preserve natural microbiota and physicochemical and organoleptic properties of food (Chowdhury *et al.,* 2023). While phage therapy offers a promising and focused approach to combating antibiotic resistant bacteria, its practical application depends on overcoming challenges related to phage persistence in the gastrointestinal tract, controlling phage release, and effectively targeting pathogens. Optimizing these factors is essential to maximize therapeutic success and facilitate its widespread application in poultry production.

The objective of this review is to assess phage therapy as a sustainable alternative to antibiotics in poultry disease management. This article will explore advanced delivery systems and encapsulation methods to improve phage effectiveness against different prevalent bacterial pathogens in poultry.

Bacterial diseases in poultry: Bacterial diseases affecting poultry are devastating not only to the health and well-being of chickens but also to the economic sustainability of poultry farming (Hafez *et al.* 2020; MartinHalder *et al*., 2021). Among the most severe bacterial diseases are salmonellosis, colibacillosis, and necrotic enteritis. These diseases vary in terms of their epidemiology, causative agents, and consequences on both poultry and human health (Lutful *et al.,* 2010; Martin *et al*., 2021). Below is an overview of these diseases, their impacts, and their public health implications.

Salmonellosis: Salmonellosis is caused by bacteria of the *Salmonella* genus, which are facultative anaerobic, gram-negative rods. These bacteria typically inhabit the intestines of poultry and spread through contaminated feed, water, or the environment (Ahmed *et al*., 2016). The most common serovars affecting poultry are *S. enteritidis* and *S. typhimurium*. The disease often remains asymptomatic in birds, which complicates containment efforts. Since salmonellosis is zoonotic, it can be transmitted to humans through the consumption of contaminated poultry meat or eggs (Yousuf *et al*., 2023).

Economically, salmonellosis leads to reduced production yields, increased mortality, and high costs associated with vaccination and stringent control measures (Hossain *et al*. 2021). From a public health perspective, the disease can cause severe gastrointestinal symptoms in humans, including diarrhea, fever, and abdominal cramps, with more serious complications in immuno-compromised individuals (Sell *et al*., 2018). Moreover, *Salmonella spp,* isolated from poultry are mainly resistant to antibiotics, leading to current treatment failures (Yasmin *et al.,* 2018). Based on the high antibiotic resistance rate in *Salmonella,* and its impact on food safety, there is an urgent need of intervention measures and proper surveillance to control antibiotic resistance.

Colibacillosis: Colibacillosis, caused by *E. coli*, is another major bacterial disease in poultry. Although *E. coli* is a part of the normal flora in healthy birds, it can become pathogenic, leading to diseases such as pneumonia, septicemia, and cellulitis (Awawdeh *et al*., 2023). The disease spreads rapidly under poor environmental conditions, such as overcrowding and inadequate ventilation in chicken houses (Lutful *et al.,* 2010).

Economically, colibacillosis results in poor feed conversion, reduced weight gain, and high mortality rates, especially in broilers. Poultry producers incur significant costs for treatment, prevention, and losses from condemned carcasses. Although its public health risk is lower than that of salmonellosis, there is growing concern over antibiotic-resistant strains of *E. coli* that can enter the human food chain (Fairbrother *et al*.,2019).

Necrotic Enteritis (NE): Necrotic enteritis (NE) is caused by *Clostridium perfringens*, a gram-positive, spore-forming bacillus, commonly found in the environment and gastrointestinal tracts of healthy birds (Fathima *et al*., 2022). NE typically develops after disruptions to the intestinal microflora, often following coccidiosis infections or the use of antibiotics, which create favorable conditions for *C. perfringens* to produce toxins that damage the intestinal epithelium. High stocking densities and high-protein diets are key risk factors contributing to NE outbreaks (Abd El-Hack *et al*., 2022).

Economically, NE inflicts significant losses on broiler production due to poor feed conversion, weight loss, and increased mortality rates. The disease can affect up to half of a flock and leads to high morbidity. Although NE is not considered a zoonotic threat to humans, it poses a considerable economic burden on poultry producers through prevention, treatment costs, and its negative impact on meat quality (McDevitt *et al.,* 2006).

Use of antibiotics in poultry and the associated disadvantages: The Egyptian Poultry Federation reports that antibiotics have been used in poultry farming since the 1950s for controlling bacterial diseases, therapeutic purposes, and as growth promoters (Azizi *et al*., 2024). These drugs have played a crucial role in maintaining the health and productivity of poultry populations. However, the excessive and improper use of antibiotics has led to significant problems, particularly the development of AMR, a critical issue for both animal and human health (Salam *et al*., 2023). Table 1 shows the list of some of the commonly used antibiotics in poultry farming, the pathogens they target, and the associated risks.

Tetracyclines and sulfonamides are among the most used antibiotics in poultry farming due to their effectiveness against bacterial pathogens such as *E. coli* and *Salmonella*. These antibiotics are frequently employed not only for therapeutic purposes but also as growth promoters, which has accelerated the development of bacterial resistance. Research indicates that residues of these antibiotics, particularly sulfonamides, remain present in poultry products, posing potential health risks to consumers (Martínez *et al*., 2018). Another group of widely used antibiotics in poultry is fluoroquinolones, which are highly effective against *Campylobacter* and *E. coli*. However, their use contributes to the transfer of antibiotic resistance to human pathogens, complicating the treatment of bacterial infections in humans (Abd El-Hack *et al*., 2022).

While antibiotics have helped to sustain the poultry industry, their overuse has contributed to the rise of antibiotic-resistant bacteria. This threatens food safety, human health, and the environment, as resistant bacteria can spread from poultry to humans through food consumption or environmental contamination. In response, alternative methods for controlling bacterial infections in poultry, such as bacteriophage therapy, have gained attention (Jiang *et al*., 2024).

Bacteriophages as an alternative to antibiotics

Mechanism of phage action: Bacteriophages, or phages, are viruses that specifically infect and destroy bacteria. Phages were discovered in the early 20th century, they have emerged as a promising alternative for combating bacterial infections, particularly in cases where antibiotic resistance poses a significant challenge (Jamal *et al*., 2019; Uddin *et al*., 2021). Phages are among the most abundant and diverse organisms on earth, with an estimated 10^31 phage particles present in environments such as soil, water, and the intestines of animals (Abedon *et al*., 2011).

Phages operate through a precise mechanism. They first bind to specific receptors on the surface of their target bacteria (Dowah and Clokie, 2018; Hussain *et al*. 2021). Once attached, phages inject their genetic material into the bacterial cell, hijacking the host's cellular machinery to replicate phage DNA and synthesize new phage particles. This process culminates in the lysis, or bursting, of the bacterial cell, releasing new phages that can go on to infect additional bacterial targets (Tian *et al*., 2021). Bacteriophages can be beneficial in treating poultry bacterial disease as compared to traditional antibiotics, as shown in Fig 1.

Advantages over antibiotics: Bacteriophages are highly selective for their bacterial hosts, significantly reducing the risk of dysbiosis and minimizing collateral damage to beneficial bacteria. This specificity makes phage therapy a targeted approach to bacterial infections (Pottie *et al*. 2024). Moreover, phages can self-replicate, potentially allowing for continuous population control without the need for frequent dosing. This self-replicating nature can enhance the long-term effectiveness of treatment (Hoyle and Kutter, 2021). Additionally, phages have a minimal ecological footprint. After eliminating their target bacteria, they decompose quickly in the environment, reducing concerns about long-term environmental effects (Salmond *et al*., 2015). In addition, bacteria can develop resistance to phages, but phages can mutate to overcome these defenses, thus maintaining their effectiveness over time (Hasan *et al.,* 2022). This co-evolutionary arms race is in stark contrast to antibiotics, where the emergence of resistance often leads to treatment failure without the opportunity for rapid adaptation.

Studies on the use of bacteriophages in poultry: Bacteriophage therapy has shown significant promise in controlling bacterial diseases in poultry, improving food safety, and enhancing bird health (Shakir *et al.,* 2024). Case studies demonstrate its effectiveness, particularly in reducing harmful pathogens like Salmonella, Campylobacter, and *E. coli*. In one study, a phage targeting *S. enteritidis* added to poultry feed significantly reduced intestinal colonization, indicating its potential as a prophylactic tool in farming (Kimminau *et al*., 2020). Similarly, *Campylobacter. coli* levels were substantially reduced when broilers were treated with a phage cocktail in their drinking water, lowering contamination risks in poultry products (Steffan e*t al*., 2022). In another case, aerosolized phages effectively treated E. coli infections, improving bird health and reducing mortality rates (Nicolas *et al*., 2023).

Beyond direct disease control, bacteriophages have been explored to enhance production and nutrient utilization in poultry. Research indicates that phages can promote body weight gain and improve feed conversion ratios, particularly by eliminating harmful bacteria such as

Salmonella and *C. perfringens*, which allows beneficial gut bacteria like *Lactobacillus* to thrive (Jiang *et al*., 2024). Additionally, when combined with probiotics, phages further improve poultry performance, supporting the development of cost-effective, sustainable solutions for the poultry industry (Islam *et al*., 2023). Moreover, Phage treatments have been proven to reduce pathogen loads in raw and processed meats, even under refrigeration, enhancing food safety throughout the supply chain. The stability of some phages across various food types and their simple application makes them a promising tool in modern food safety management (Vikram *et al*. 2023). These findings underscore the potential of phages as a natural, targeted alternative to antibiotics in industrial poultry production (Garvey *et al*., 2022). Several phages targeting pathogens like *Campylobacter*, *Salmonella*, and *E. coli* are listed in Table 2.

Use of phage-derived enzymes: Endolysins and holins are key components in the bacteriophage life cycle, specifically involved in breaking down the bacterial cell wall. In addition to whole bacteriophages, these phage-derived proteins are also being explored for their antibacterial properties (Grabowski *et al*., 2021).

Endolysins are enzymes produced by bacteriophages during the early stages of bacterial cell lysis. These enzymes degrade the bacterial cell wall, facilitating the release of new phage particles by lysing the host cell. Due to their ability to specifically target and break down bacterial cell walls, endolysins are being investigated as

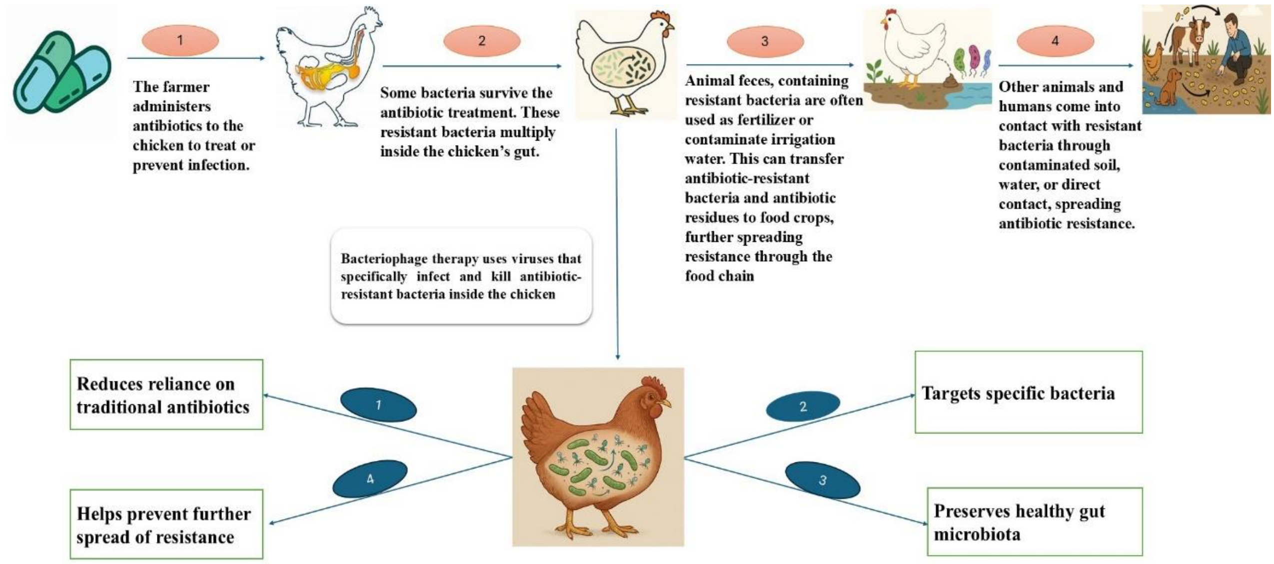

Fig 1: Mechanism of antibiotic spread in poultry and the importance of bacteriophage therapy. This figure shows how antibiotic resistance spreads in poultry through overuse and environmental contamination. It highlights bacteriophage therapy as a targeted alternative to combat antibiotic-resistant bacteria while preserving healthy gut microbiota and reducing reliance on traditional antibiotics.

Table 1: Commonly used antibiotics in poultry and associated drawbacks

Antibiotic	Target Pathogen	Purpose	Associated drawbacks
Tetracyclines	*E. coli*, *Mycoplasma* spp.	Treatment and growth promotion	Development of resistant bacterial strains (Smith and Coast, 2013)
Sulfonamides	*Salmonella* spp., *E. coli*	Treatment of infections	Persistence of residues in meat and eggs (Hassan *et al*., 2021)
Fluoroquinolones	*Campylobacter* spp., *E. coli*	Treatment of respiratory and enteric diseases	Transfer of resistance to human pathogens (Campos A, 2021)
Macrolides	*Mycoplasma* spp., *Clostridium* spp.	Treatment of respiratory infections	Potential for cross-resistance with other antibiotics (Founou *et al*., 2016)
Aminoglycosides	*E. coli*, *Pseudomonas* spp.	Treatment of severe infections	Toxicity and environmental contamination (Kemper, 2008)
Beta-lactams (Penicillins)	*Staphylococcus* spp., *Streptococcus* spp.	Treatment of Gram-positive bacterial infections	Reduced effectiveness due to widespread resistance (Gouvêa *et al*., 2015)

Table 2: Bacteriophage isolated against poultry pathogens and their effectiveness.

Bacteriophage	Target Pathogen	Application Method	Effectiveness	Citation
PHL4	*S. enteritidis*	Spray Application on Carcasses	Significant reduction in *Salmonella* colonization	(Higgins *et al*., 2005)
vB_CcM	*Campylobacter jejuni*, *Campylobacter coli*	Water supply	Decreased *Campylobacter* levels in broilers	(Steffan *et al*., 2022)
CEV1	*Escherichia coli O157:H7*	Oral Delivery	Reduction in intestinal *E. coli* O157:H7 levels	(Raya *et al*., 2006)
F01-E2	*S. typhimurium*	surface of various RTE food products	Complete elimination of viable *Salmonella* from food products	(Von et al., 2013)
CP220	*Campylobacter coli* and *Campylobacter jejuni*	Oral gavage	Decreased *Campylobacter* colonization in chickens	(El-Shibiny *et al*., 2009)
ECML-4	*Escherichia coli*	Applied on contaminated foods	Effective reduction of *E. coli* in different foods	(Abuladze *et al*., 2008)
UAB_Phi20	*Salmonella spp.*	In vivo oral route	Reduced *Salmonella* prevalence in treated birds	(Colom *et al*., 2015)

potential antimicrobial agents. They are particularly effective against Gram-positive bacteria because their peptidoglycan layer is more accessible to endolysins, enabling rapid bacterial eradication without the need for viral reproduction (Lu *et al*., 2020).

On the other hand, Holins are small proteins, that play a pivotal role in the bacteriophage life cycle, by forming pores in the bacterial cell membrane. These pores allow endolysins to access and degrade the bacterial cell wall. Holins are also being studied for synthetic biology and biotechnological applications. Due to their ability to regulate membrane permeability, holins offer potential for timed and controlled release of antimicrobial or therapeutic molecules in bacterial cultures (Young *et al*., 2014).

Encapsulation technologies for phage delivery in poultry: Due to its lower pH, encapsulation of bacteriophages can be used to combat the rapid deactivation of free phages in the chicken stomach for better delivery to poultry gut. The protection provided by encapsulation allows phages to remain viable, until they reach the target site of infection, which improves their efficiency in treating diseases. In addition, it allows the accurate distribution of phages (Vinnerås *et al.,* 2021). Phages protected by encapsulation remain more stable during storage and feed processing. This technique is necessary to take advantage of phage therapy for safe, effective and permanent solutions for bacterial infections, and antibiotic resistance in poultry (Abbas *et al.,* 2022). Various encapsulation strategies have been developed to enhance the delivery of bacteriophages to treat bacterial infections in poultry. Key formulations include:

Alginate as a primary encapsulation medium: Alginate is a natural polysaccharide that serves as an effective primary encapsulation medium for phages due to its biocompatibility and hydrogel-forming capabilities (Pérez-Luna *et al*., 2018). It significantly enhances phage survival rates, allowing more active phages to reach the gastrointestinal tract to combat pathogens like Salmonella and Campylobacter (Gomez-Garcia *et al*., 2021). Its affordability and low toxicity contribute to its popularity as a biopolymer for phage encapsulation (Sharma *et al*., 2024).

Early research utilized an ionic gelation method with calcium as a cross-linking agent, demonstrating that encapsulated *Salmonella* phage Felix O1 remained infectious in the gastrointestinal tract (Ma Yongsheng *et al*., 2008). Soto et al., 2018, reported that phages encapsulated in calcium alginate outperformed non-encapsulated phages in a simulated water flow system, maintaining viability for an additional 100 hours, which is crucial for poultry applications. Pereira *et al*., 2023, successfully encapsulated a cocktail of lytic phages, against *Salmonella enterica* in calcium alginate microparticles for treating salmonellosis in chickens.

Other strategies include encapsulating phages, targeting *Salmonella Senftenberg* (nontyphoidal *Salmonella* serotype), within an Eudragit™ L100 polymer and trehalose system (Lorenzo *et al*., 2022), as well as using xanthan-alginate-$CaCl_2$ particles with chitooligosaccharides, for *Salmonella enteritidis* delivery (Zhang *et al*., 2023). Additionally, alginate combined with whey protein has been applied for phage delivery against *S. typhimurium* (Alves *et al*. 2020; Lorenzo-Rebenaque *et al*., 2022). While alginate protects phage from harsh stomach conditions and facilitates targeted intestinal release, ongoing research is focused on improving encapsulation stability and controlling phage release dynamics. The favorable regulatory profile, low toxicity, and cost-effectiveness still make it the leading practical phage delivery system for poultry health.

Chitosan encapsulation: Chitosan, derived from chitin, is another biopolymer utilized for phage encapsulation. Its positive charge enhances attraction to negatively charged bacterial membranes, improving phage attachment and entry. Studies indicate that chitosan-encapsulated phages maintain stability and activity for extended periods, making them suitable for use in poultry feed (Elsayed *et al*., 2024). Chitosan-based microbeads were also used for treating colibacillosis in chickens (Kaikabo *et al*., 2017). Based on its biocompatibility, and demonstrated ability to encapsulate different biological agents, chitosan is a promising and suitable biomaterial for surface coating and delivery of bacteriophages in poultry disease prevention.

Liposome-based encapsulation: Liposomes serve as lipid-based carriers that can encapsulate phages, providing protection from environmental damage. They also enhance phage stability, allowing for prolonged functionality in the gastrointestinal tract (Pinilla *et al*., 2021). Colom *et al*., 2015, compared the efficacy of liposome-encapsulated phages against non-encapsulated counterparts in broilers, highlighting the advantages of liposome-encapsulated phages (Colom *et al*., 2015). Several studies have shown that liposome-encapsulated bacteriophages demonstrate promising biodistribution. Liposome encapsulation has been shown to increase phage stability in the stomach and improve intestinal epithelial binding. In mice, encapsulated phages were detectable up to 72 h after exposure, whereas uncoated phages declined rapidly (Otero *et al.,* 2019). With their ability to protect phages from harmful gastrointestinal conditions and improve their clinical efficacy, liposomes have emerged as a promising carrier system for bacteriophages in poultry applications.

Nano-carriers for phage delivery: Nano-carriers represent a significant advancement in phage therapy delivery, providing protection against degradation and improving targeting capabilities (Paczesny *et al*., 2020). Polymeric nanoparticles, specifically poly (lactic-co-glycolic acid) (PLGA), can be designed to encapsulate phages. These biodegradable nanoparticles can be programmed for timely phage release when targeted microbes are present in the gut, thereby enhancing therapeutic effectiveness while minimizing the required dosage (Yan *et al*., 2021).

Research into gold nanoparticles has also gained traction, as these can act as vectors for phages, enabling targeted delivery to specific areas of the colon and offering protection from environmental degradation (Rosero *et al*., 2024). Furthermore, gold nanoparticles can be modified to enhance their targeting capacity, further improving the efficacy of phage therapy. By facilitating delivery, enhancing mucosal targeting, and protecting against environmental stress, nanocarrier systems, particularly

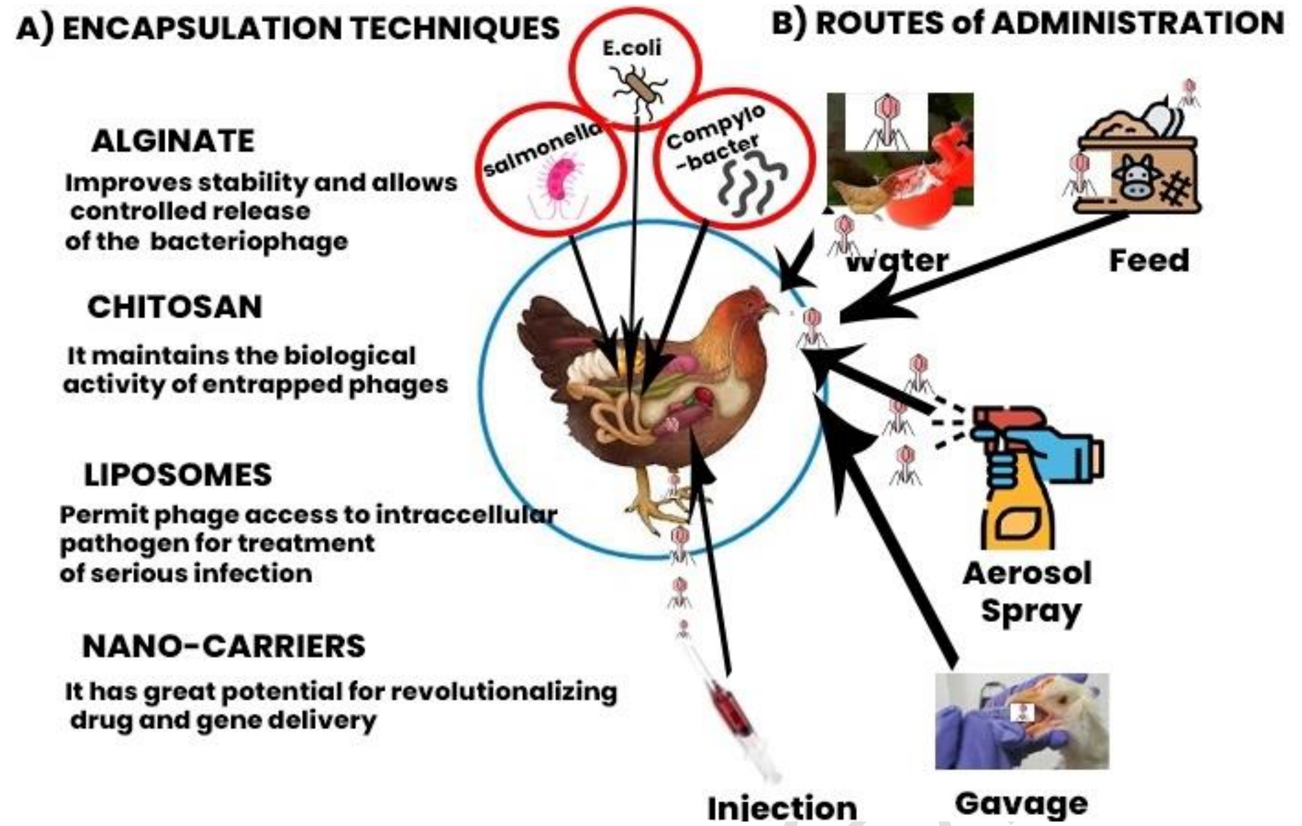

Fig 2: This figure highlights A) Encapsulation Techniques and B) Routes of Administration for bacteriophage delivery in poultry disease management. In A, various encapsulation techniques such as alginate, chitosan, liposomes, and nano-carriers improve phage stability, control release, and target pathogen access. In B, the routes of administration include water, feed, aerosol spray, injection, and gavage, all aiming to effectively deliver bacteriophages to combat pathogens like *Salmonella*, *E. coli*, and *Campylobacter*, enhancing poultry health and food safety.

PLGA and gold nanoparticles, represent a high-throughput approach to improve phage delivery and safe administration in poultry (Saha *et al.*, 2022). Figure 2 depicts various phage delivery polymers and their routes of administration.

Novel formulations for phage therapy: Recent advancements in phage therapy include the development of novel formulations that combine bacteriophages with other bioactive compounds to enhance their antimicrobial activity (Rajendran *et al*., 2022).

Phage-prebiotic combinations: Integrating phages with prebiotics, such as inulin or fructo-oligosaccharides, not only inhibits pathogenic bacteria but also promotes the growth of beneficial gut microbiota. This dual approach improves both phage therapy efficacy and gut health (Peng *et al*., 2019).

Synergy with antibiotics: Phages can be used in conjunction with antibiotics to enhance therapeutic efficacy and mitigate the risk of developing antibiotic resistance. This synergistic approach can lead to improved treatment outcomes. In phage-antibiotic synergy, mainly antibiotics disrupt the bacterial structure and may increase bacterial susceptibility to phage infection. In addition, phages can disrupt biofilms allowing better antibiotic penetration, and the combination can re-sensitize antibiotic-resistant bacteria to drugs (Knezevic *et al*.2019; Luong *et al*., 2020).

Phage-enhanced feed additives: Phages are often administered to animals orally as feed additives, in water, or via gavage. However, gavage is impractical, in intensive farming settings. Phages are unstable in the acidic environment of the stomach, which complicates oral delivery. To address this, studies recommend combining phages with buffering agents to enhance stability (Vandenheuvel *et al*., 2015).

Ethical implications and analysis of bacteriophage therapy: The large-scale application of bacteriophage therapy raises several ethical and legal challenges that need to be addressed to ensure its safe and effective use.

Safety Concerns: The use of live viruses as therapeutic agents raises significant biosafety issues, including the potential interactions between viral vectors and host organisms or the environment. Regulatory bodies must ensure that any bacteriophage used in therapy is well-characterized and rigorously investigated to avoid harming patients (Merabishvili *et al*., 2019).

Phage resistance: Just as bacteria can develop resistance to antibiotics, they can also become resistant to phages. This possibility necessitates careful management of phage application to prevent the emergence of phage-resistant bacterial strains (Labrie *et al*., 2010).

Environmental impact: Phages are naturally occurring entities, but their widespread use could impact ecological systems. Research is needed to assess the long-term effects of phage therapy on environmental niches and ecosystems (Weinbauer, 2004).

Conclusion and future perspectives: This review highlights the significant challenges posed by bacterial diseases in poultry, exacerbated by the rise of AMR. Bacteriophage therapy emerges as a promising alternative to antibiotics, offering targeted action against harmful bacteria while preserving beneficial gut microbiota. Innovative delivery systems and encapsulation techniques further enhance the stability and effectiveness of phages in poultry applications. While promising field studies indicate the potential of phage therapy in reducing bacterial loads and improving poultry health, its successful implementation requires addressing ethical, safety, and regulatory concerns. With appropriate frameworks in place, phage therapy could play a vital role in advancing poultry disease management and mitigating the impact of AMR, ultimately leading to safer poultry products and improved public health outcomes. Future research should focus on refining bacteriophage delivery methods, ensuring regulatory approval, and assessing long-term safety. Investigating phage therapy's broader applications in poultry production and exploring its integration with other management strategies will be essential to maximize its potential and improve both animal health and food safety.

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