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Review Article

Bacteriophage therapy for controlling poultry production problems

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Abstract

Today, many poultry production systems require no antibiotics ever. Due to the unavailability of novel antibiotics for veterinary use, presence of multidrug resistant bacteria, and official banning of many antibiotic classes for use in veterinary medicine for production animals, the need for alternative therapeutics such as competitive exclusion compounds, vaccines, nano-medicine, etc. has become an urgent need. In this context, bacteriophages are regarded as an antibiotic alternative. Bacteriophages are viruses that target to infect, replicate, and lyse numerus types of bacteria in humans, animals, water, plants, and food. They are classified into several orders and 15 families. Different preparations of bacteriophages have been approved by the United States of Food and Drug Administration for managing some bacterial infections. They have been globally used in the poultry production and processing. Therefore, the present review intends to expose every aspect of bacteriophages in poultry health and production which include the mechanisms of phages as therapeutics, their usage in the industry, and the limitations/threats associated with the usage of bacteriophages.

Key words: Bacteriophages, Chickens, Immunity, Limitations, Performance

Introduction

Antimicrobials have been applied since the 1940s for controlling human and animal's bacterial infections. They have also been used as feed additives growth promoters to enhance the production performance parameters and reduce mortalities of animals (Moore *et al*., 1946). Nevertheless, usage of these types of antibiotics is usually associated with the development of multi-drug resistance bacteria that pose a public health threat (Mund *et al*., 2017). Therefore, the application of antimicrobial growth promoters has been banned since 2006 and researchers have been encouraged to look for safer alternatives (bio-control agents) (Abd El-Ghany, 2023, 2024). Bacteriophages can be used as a safe, effective, and promising alternative to antibiotics in livestock and poultry production sectors (Gadde *et al*., 2017; Xu *et al*., 2018; Gigante and Atterbury, 2019; Thanki *et al*., 2019; Sarrami *et al*., 2022). They have been approved and have officially become commercially available for use in some countries. Some commercial bacteriophages showed effectiveness and were approved by the United States Food and Drug Administration (U.S. FDA) for managing of multidrug resistance problems in poultry industry (Doffkay *et al*., 2015; Wernicki *et al*., 2017; Moye *et al*., 2018).

Bacteriophages were discovered in the early 1900s by Twort in 1915. The first detection of phage efficacy showed its ability to increase the survival of chickens against fowl typhoid by 95-100% compared with 0-25% in untreated control chickens (Duckworth, 1976). Bacteriophages are viruses that target, infect, and propagate intracellularly, and then lyse specific prokaryotes (bacteria) or arachea cells (Bren, 2007; Wernicki *et al*., 2017). They are ubiquitous on earth with estimated numbers 10 times greater than bacterial cells (Gómez-Gómez *et al*., 2019). Phages are found in water, plants, and food, and therefore are frequently consumed by humans without pathogenicity (Clokie *et al*., 2011).

Despite bacteriophages are obligate parasites of bacteria, they are not able to replicate independently. They act specifically to infect bacteria and most of them can infect only one or a limited number of bacterial species (Ly-chatain, 2014). Bacteriophages are highly specific towards their hosts with a limited host range (Lu *et al*., 2003; Carey-smith *et al*., 2006; Naghizadeh *et al*., 2018) and have a specificity for the bacterial species. Because of their ability to self-replication, they do not need to be applied repeatedly. Besides, bacteriophages are mostly made up of proteins and nucleic acids, thus they are non-toxic (Loc-Carrillo and Abedon, 2011).

They are almost a hundred times smaller than cells of

bacteria, and only infect a subgroup of bacterial strains within a host species. They are divided into numerous orders and approximately 15 families. Moreover, more than 5,000 phages have 20-200 nm isometric heads and tails and they can be viewed under the transmission electron microscope (Adriaenssens and Rodney Brister, 2017), over 96% of them have tails, and mostly they belong to the order Caudovirales. Tailed phages are divided to Siphoviruses, myoviruses, and podoviruses which were represented by 61%, 25%, and 14%, respectively (Ackermann, 2011). Phages belong to Caudovirales are 1000 times smaller than the bacterium (0.5-20 µm) (Ackermann, 2011).

Bacteriophages are present in the surrounding environment in large numbers and have the ability to eliminate infectious diseases (Brüssow, 2005). They have shown a promising activity against both Gram-positive and Gram-negative bacteria, including the drug resistant strains. Moreover, they have a selective elimination of bacterial pathogens (Fernandes *et al*., 2012). Phages can effectively lower the bacterial count (Lin *et al*., 2017) and manage some zoonotic pathogens, which significantly impact public health (Gill, 2016; European Food Safety Authority, 2017; Moye *et al*., 2018). For example, bacteriophages are used for the treatment of combined infections by *Staphylococcus aureus*, *Escherichia coli*, *Proteus* spp., *Klebsiella* spp., *Pseudomonas* spp., and vancomycin-resistant *Enterococci* in humans (Biswas *et al*., 2002). Despite, little is known about the healthy chicken gut phageome, bacteriophages have shown effectiveness for treatment of poultry pathogens approved by FDA (Żbikowska *et al*., 2020) that includes *E. coli*, *Clostridium perfringens* (Miller *et al*., 2010), *Salmonella* spp. (Carey-smith *et al*., 2006), *Campylobacter jejuni* (*C. jejuni*) (Richards *et al*., 2019), and *S. aureus* (Marek *et al*., 2019). A robust body of evidence showed that phages can be used at several points from farm-to-fork for controlling pathogens (Sillankorva *et al*., 2012; Hussain *et al*., 2017). Only the lytic bacteriophages are applied to treat bacterial infections and appropriate for phage therapy. They are able to lyse infected bacteria and mutate resistant ones. However, commensal gut microbiomes are not demolished by bacteriophages. In addition, phages could be naturally implemented in food security during processing or packaging (Endersen *et al*., 2014; Gouvêa *et al*., 2016; Vikram *et al*., 2021). Phage cocktails were used for controlling *C. jejuni* (Chinivasagam *et al*., 2020) and *Salmonella* Enteritidis (Nabil *et al*., 2018) infections in broiler chickens from the farm to the processing plant.

In comparison with antibiotics, bacteriophages are significantly more specific to the bacterial serotypes and strains, do not alter the gut microflora, nor increase the risk of dysbiosis, immunosuppression, and secondary infections. However, some difficulties interfere with the bacteriophages applications in commercial production systems (Hietala *et al*., 2019; Cazares *et al*., 2020) such as the narrow spectrum activity that can be a problem in a disease control in different infection types (Barrow *et al*., 1998).

Therefore, the present review was intended to cover the mechanisms of phages as therapeutics, their usage in the industry, and limitations/threats involved with the usage of bacteriophages.

Replication cycle and spectrum of bacteriophages

The tail of the bacteriophage should recognize the matching bacterial antigen for the attachment and binding to the surface receptors of the bacterium. The replication of a bacteriophage occurs through the lytic or lysogenic cycle. The structure of bacteriophage is illustrated in Fig. 1.

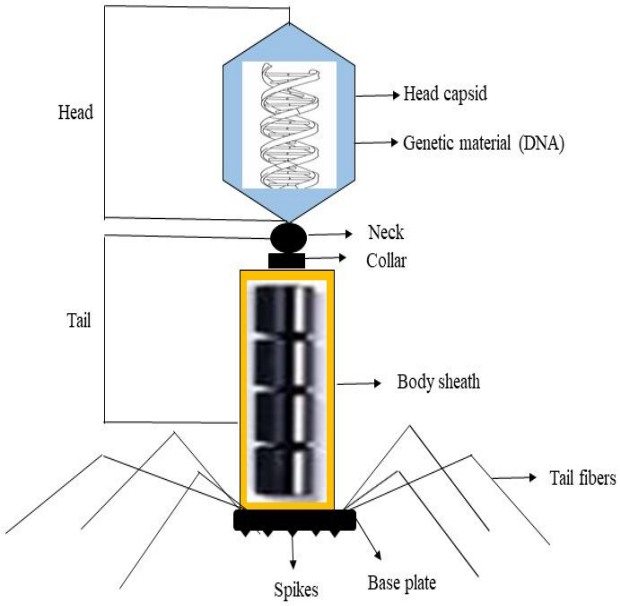

Fig. 1: Structure of a bacteriophage

In the lytic cycle, bacteriophages tails fibers attach to the bacterial cells surface receptors, inject their DNA or RNA into the bacterial genome, and stimulate the host's metabolic processes to produce more phage virions which consequently help in the cell lysis and release of the virions for further infections cycles (Clokie and Kropinski, 2009). Bacteriophages use organelles and enzymes of the infected bacterial cells for replication of the injected genetic materials and production of more phages that released after the bacterial lysis (Akhtar *et al*., 2014). Therefore, lytic bacteriophages are the best for therapeutic treatment of bacterial infections as they directly kill the target bacterial cells (Woźnica *et al*., 2015; Grant *et al*., 2016). On the other side, the DNA of bacteriophages is combined to the host bacterial cells and they are replicated together throughout the lysogenic cycle. The DNA sequencing and integrases as well as other genes of the integration process are helpful for the detection of bacteriophages life cycle (Żbikowska *et al*., 2020).

Bacteriophages get into the hosts circulation within 2-4 h following ingestion, and then they could be

detected in some internal organs such as liver and spleen approximately 10 h after ingestion (Ly-chatain, 2014). However, they could be eliminated rapidly from the internal organs and blood stream by phagocytic cells. In addition, bacteriophages are also cleared by the reticulo-endothelial system in the liver and spleen of the host cells (Cisek *et al*., 2017).

The broad host-range bacteriophages provide a broader lytic scope and they are more preferable than narrow host range types. Thus, the broad type are used as therapeutics against many strains of the target bacteria (De Jonge *et al*., 2019). Multiple bacteriophages can be collected as a cocktail to increase the bacteriophages coverage of the target species (Chan *et al*., 2013).

Regulations of bacteriophages production

Bacteriophages have different intervention applications both in humans and animal therapies (Fig. 2); thus, their products require regulatory efficacy and safety roles for application in the market. Bacteriophages production are regulated by FDA, regardless of whether their use in humans or animals or their natural or engineered origin. The bacteriophages are also presently regulated in Europe by the European Commission through the European Medicines Agency. Unlike the US system, the genetically altered phages are regulated differently in the European countries. Moreover, in the United Kingdom, phages are regulated by the Veterinary Medical Directorate for those used in animals, by the Medicines and Healthcare products Regulatory Agency (MHRA) for those used in medicine, and by Food Standards Agency for those used in food. There are parallels of regulatory agencies with other biologicals for effective regulation of bacteriophages production (Fauconnier, 2019).

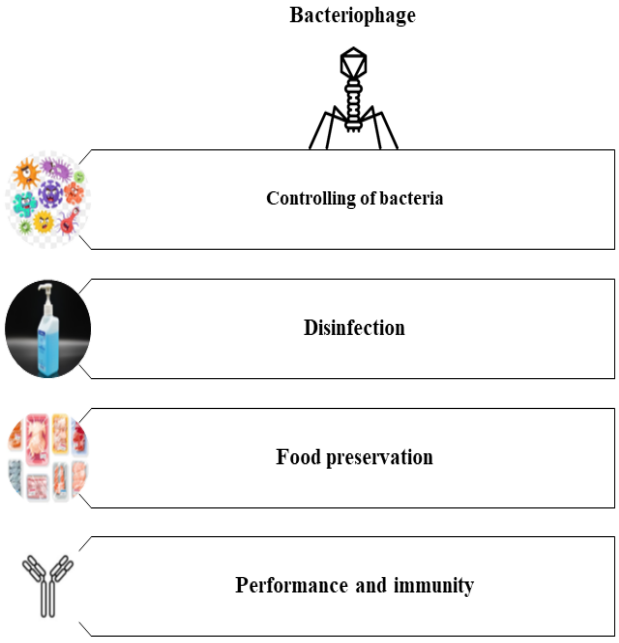

Fig. 2: Different intervention applications of bacteriophages

Factors affecting the efficacy of bacteriophages in poultry industry

Bacteriophages preparation, dose, timing of administration, and the concurrent use with other compounds or vaccines should be taken in consideration before their application in poultry production system. Moreover, the improvement of phages selection, isolation, designing, purification, and adaptation methods are important to obtain their optimal efficacy (Garcia *et al*., 2008).

The environmental factors such as temperature is critical for the persistence of bacteriophages in/on food. The suitable temperatures for bacteriophages stability vary and they should be tested to determine which are more effective during food storage. It has been reported that refrigeration temperatures can enhance phages persistence on the meat products surfaces (European Food Safety Authority (EFSA), 2009).

The addition of different phages (cocktails) to the same product can broad the lytic spectrum, delay the bacterial resistance, and consequently increase therapy effectiveness (Wernicki *et al*., 2017). Lysogenic phages with known nucleotide sequences as well as strong and specific types are preferable. It is important to understand how the phage genes flow into their hosts, to avoid the possible undesirable types and to prevent the horizontal transfer of the undesirable traits or any other genes to bacteria, animals, or humans via the food chain. In addition, phages should be sterile and free from any residual endotoxins that induce allergic conditions.

The interaction between phages and the host immune system is not well understood. Therefore, it is so critical to screen phage's ability to avoid the possibility of antibody neutralization (Naghizadeh *et al*., 2019). Some phages induce no-phage antibodies in the serum of humans (Bruttin and Brüssow, 2005) or chickens (Abbas *et al*., 2022). Nevertheless, the later work detected different levels of antibodies after phage therapy (Łusiak-Szelachowska *et al*., 2014; Zaczek *et al*., 2016; Majewska *et al*., 2019). Sometimes, the phage-antibody interactions do not result in the inactivation of bacteriophages. Phage encapsulation process has been developed to improve the safety and efficacy especially when added to the food products or animals feed (Choińska-Pulita *et al*., 2015). A recent study by Sarrami *et al*. (2022) showed that bacteriophages (1-1.5 g/kg diet) could modulate and boost the immunity and performance of broiler chickens through the up-regulation of gut *interleukin* (*IL*)-10 gene, activation of the downstream signaling pathways, enhancing the up and down-regulation of *PPARγ* and *PGC-1α* genes, and consequently improving the epithelial cells metabolism.

Applications of bacteriophages

Controlling of bacterial infections

The scheme of the antibacterial mechanism of bacteriophage is shown in Fig. 3.

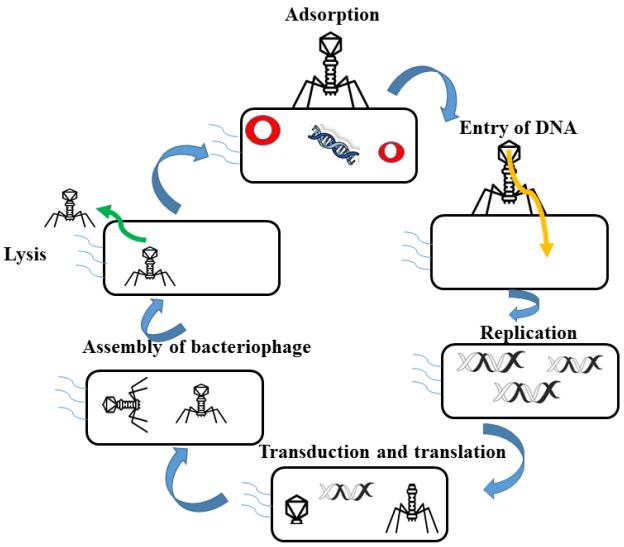

Fig. 3: Scheme of the antibacterial mechanism of bacteriophage

Salmonella spp.

The different types of *Salmonella* spp. are very important and significant bacterial pathogens that adversely affect the poultry production with a public health concern (Abd El-Ghany, 2020). In poultry, *Salmonella* spp. are categorized intro 2 main groups; host-specific typhoid infections caused by non-motile *S.* Pullorum and *S.* Gallinarum as well as non-host-specific paratyphoid infections caused by motile *S.* Enteritidis, *S.* Typhimurium, *S.* Kentucky, *S.* Heidelberg, *S.* Infantis, *S.* Hadar, *S.* Anatum, *S.* Virchoff, etc. Infections with *S.* Pullorum and *S.* Gallinarum induce either acute systemic disease in young birds or asymptomatic infections in adult carriers. Paratyphoid infections may cause persistent colonization of the gut and internal organs, possibly lead to contamination during carcasses processing. However, in highly susceptible stressed young birds, paratyphoid infection is an acute and systemic. For instance, *S.* Arizonae is an acute or chronic disease of turkey poults, but adult birds are carriers without signs (Gast, 2013). In 2017, the European Union reported human cases with *S.* Enteritidis (20.1 cases per 100,000 inhabitants). Most of the reported human's food born outbreaks were caused by consumption of contaminated chickens' meat or eggs and egg products [European Food Safety Authority (EFSA), 2017].

Salmonella-specific bacteriophages have been isolated from excreted sewage, environmental drag swabs, fecal material of chicken's farms, food processing plants, and wild boar reserve (Andreatti Filho *et al*., 2007; Bao *et al*., 2011; Rahaman *et al*., 2014; Thanki *et al*., 2019). The adjustment of bacteriophages treatment conditions may make it possible to use just one or two bacteriophages rather than many (Atterbury *et al*., 2007). The bacteriophages cocktails have more lytic effect on *Salmonella* spp. than a phage alone. It has been reported that several oral treatments with bacteriophage cocktails obtained from *S.* Enteritidis and *S.* Typhimurium could promote the lysis of *S.* Virchow, *S.* Hadar, and *S.* Infantis and induce a significant reduction of *Salmonella* count in the cecum of chickens (Bardina *et al*., 2012). In addition, Nabil *et al.* (2018) recommended 5 successive bacteriophage treatments doses (one pre- and 4 post-*Salmonella* infection) for complete clearness of the intestinal bacterial load in chicks. A combination of bacteriophages and chemical treatments reduced *Salmonella* counts to below detection levels (Sukumaran *et al*., 2015).

The different effects of bacteriophages treatments on *Salmonella* spp. are illustrated in Table 1. Over the last decade, many bacteriophages have been produced against *Salmonella* spp. infections (Monk *et al*., 2010; Moye *et al*., 2018). It has been found that a commercial product containing bacteriophage was able to reduce mortality and *Salmonella* counts as much as 200 times and improve the feed conversion rate when used as a prophylactic or a post-*Salmonella* infection intervention strategy (Wójcik *et al*., 2015). Multiple doses of a bacteriophage mixture in the chickens' drinking water were safe and did not affect behavior or the production parameters, and significantly decreased the bacterial load in the droppings of birds at the end of the study (Clavijo *et al*., 2019). Moreover, Sklar and Joerger (2001) reported that the process of mixing phage with feed and storing feed over 14 days caused a 2 $\log_{10}$ PFU/g reduction in phage numbers. The presence of bacteriophages during the *in vivo* studies should be verified by their isolation from cecal contents of treated chickens (Fiorentin *et al*., 2005).

Bacteriophages were effective in reducing *S.* Gallinarum in layer chickens. The addition of bacteriophages to the feed of infected layer chickens reduced the mortality rate to 5% when compared with 30% in control non-treated chickens (Lim *et al*., 2011). Moreover, Kim *et al.* (2016) reported that treatment of broilers and breeder chickens with a bacteriophage feed additive product could control both *S.* Pullorum and *S.* Gallinarum infections and reduced the mortality rate in the challenged birds when compared with the non-phage treated control. The brown layer chickens showed improved performance and increased egg production and egg mass (following phage treatment). In the study of Hong *et al.* (2013), the oral administration of bacteriophages 7-days prior-challenge and 21 days post-challenge with *S.* Gallinarum significantly reduced the mortality rate and the bacterial re-isolation from the organs of the treated and contact non-challenged hens. But, the re-isolation rate of *S.* Gallinarum from the contact non-phage treated hens was less than that from the challenged chicken.

Campylobacter spp.

Commercial poultry and their products are natural reservoirs for *Campylobacter* spp. and they represent the major sources of human infections (Young *et al*., 2007). The prevalence rate of *Campylobacter* spp. in the commercial poultry flocks varied from 2% to 100% (Sahin *et al*., 2015). In poultry slaughter houses, 100% of small intestine and 91.5% of carcass surfaces swabs were

Table 1: The different effects of bacteriophages treatments on *Salmonella* spp.

Type of bacteria	Dose of bacteriophage	Species of birds	Effects	Reference
S. Typhimurium (10^8 CFU)	10^{12} PFU/ml	Oral therapy of day-old Rhode Island Red chickens	↓ Bacterial viability in the cecum for up to 12 h post-infection ↓ Bacterial count more than one $\log_{10}$ in crop and small intestine at the 3rd day post-treatment ↓ MR to 20% when compared to 56% in non-treated chickens	Berchieri *et al*. (1991)
S. Enteritidis (10^4 CFU)	Single phage or bacteriophages cocktail (10^7 PFU/g)	Feed treatment of broiler chicks	↓ Cecal bacterial colonization by 1.9 $\log_{10}$ CFU/g for the single and 0.6 $\log_{10}$ CFU/g for the cocktail	Sklar and Joerger (2001)
S. Enteritidis	10^5 PFU/ml	Chicken carcass	↓ Bacterial number by over 98% and bacteriophages amplified by 3-fold over 48 h	Goode *et al*. (2003)
S. Enteritidis	3-bacteriophages cocktail (10^{11} PFU/g)	Single oral treatment of broiler chickens	↓ Cecal bacterial colonization by 3.5 log units	Fiorentin *et al*. (2005)
S. Enteritidis (20 CFU/ml	10^8 and 10^{10} PFU/ml	Chicken carcass	↓ Bacterial number on contaminated chicken carcasses (1 out of 15 carcasses was positive 24 h post-treatment)	Higgins *et al*. (2005)
S. Typhimurium (10^5 CFU/ml)	3-bacteriophages cocktail (5.4×10^6 PFU/bird)	Oral treatment for 4, 5, 6, 8, 9, and 10-day-old chickens	↓ Cecal bacterial colonization by 10-fold The phage could be detected in droppings 48 h post-treatment ↑ Weight gain	Toro *et al*. (2005)
S. Enteritidis or *S*. Typhimurium	10^{11} PFU/ml	Broiler chickens	↓ Cecal bacterial colonization by 4.2 (*S*. Enteritidis) and 2.2 (*S*. Typhimurium) $\log_{10}$ CFU/ml	Atterbury *et al*. (2007)
S. Enteritidis (2.95×10^5 CFU/ml)	3-bacteriophages cocktail (10^8 PFU/ml/dose)	Two daily doses in 6-days old chicks using an aerosol spray and a probiotic at a day-old of age by coarse spray	↓ Cecal intestinal colonization Complete reduction of deaths	Borie *et al*. (2009)
S. Enteritidis (5×10^7 CFU)	10^9 PFU/g	Feed treatment of broiler chicks for 21 days	Inhibit intestinal bacterial multiplication	Lim *et al*. (2012)
S. Enteritidis (10^7 CFU/ml)	Different bacteriophages cocktails (10^9 PFU/ml) 1 h post-challenge	Oral gavage of broiler chickens	↓ Cecal bacterial counts by 2 $\log_{10}$ CFU/ml within 12 h and crop *Salmonella* count below the detectable level	Gonçalves *et al*. (2014)
S. Enteritidis	10^9-10^{10} PFU/ml	Oral treatment of 33-day-old quails for 3 days	Complete bacterial elimination from the cecal tonsils after 6 h of treatment	Ahmadi *et al*. (2016)
S. Typhimurium and *S*. Enteritidis	1.18×10^{11} PFU	Oral treatment of broiler chick	↓ bacterial cecal colonization	Nabil *et al*. (2018)
S. Enteritidis and *S*. Typhimurium (10^5 CFU)	5-bacteriophage cocktail (10^9 PFU)	Chicken breast muscles	↓ Counts of both strains by 1.6 $\log_{10}$ CFU/piece of muscle after storage at 8°C and by 3.1 and 2.2 $\log_{10}$ CFU/piece, respectively at 25°C	Duc *et al*. (2018)
Salmonella	6-bacteriophage cocktail (10^8 PFU/ml)	Drinking water treatment of broiler chickens at ages 18, 26, and 34-days	↓ Cecal bacterial count under the detectable level The mortality, productivity parameters, and the microbiome were the same for both treated and non-treated control	Clavijo *et al*. (2019)
S. Enteritidis and *S*.	10^9 PFU/ml	Spraying chicken	↓ *S*. Enteritidis and *S*.	Atterbury *et*

Typhimurium (10^6 CFU/ml)		carcasses	Typhimurium surface contamination levels by 72.2% and 38.9%, respectively	*al*. (2020)
Salmonella	10^6 and 10^7 PFU/ml	Chicken carcasses	The bacterial count reducing effect of bacteriophages was not changed following treatment at 4°C and 25°C	Yan *et al*. (2020)

CFU: Colony forming units, PFU: Plaque forming units, and MR: Mortality rate (↓ reduced and ↑ increased)

Table 2: The different effects of bacteriophages treatments on some bacterial infections

Type of bacteria	Dose of bacteriophage	Species of birds	Effects	Reference
C. jejuni (chickens and humans' origin)	10^{7-9} PFU/ml	Oral treatment of 25-day-old broiler chickens	↓ Gut and cecal colonization (0.5 to 5 log units)	Loc-Carrillo *et al*. (2005)
C. jejuni (1×10^5 CFU)	$0.4\text{-}2 \times 10^9$ PFU/ml	Oral treatment of 10-day-old broiler chickens	Inhibit cecal bacterial colonization post-treatment of infected chickens	Wagenaar *et al*. (2005)
C. jejuni and *C. coli*	10^7-10^9 PFU/ml	Oral treatment of broiler chickens for 5 days	↓ *C. jejuni* and *C. coli* intestinal count after 48 h of administration	El-Shibiny *et al*. (2009)
E. coli (10^3 CFU)	10^3 PFU /ml 10^4 PFU /ml 10^8 PFU /ml	Water or aerosol spray treatment for a week-old broiler chickens	↓ MR to 25% (10^3 PFU/ml) and 5% (10^4 PFU/ml) No MR (10^8 PFU/ml)	Huff *et al.* (2002)
E. coli (10^4 CFU)	2-bacteriophage cocktail (2.6×10^8 and 2.35×10^9 PFU/ml)	Aerosol treatment of 10 days to 2-week-old broiler chickens	↓ MR (20-27%) ↓ Respiratory signs related infection	Huff *et al.* (2003)
E. coli	2-bacteriophage cocktail (10^9 PFU/ml)	Intramuscular injection of cocktail and water treatment with enrofloxacin in broiler chickens	↓ MR to 15% in treated chickens compared to 68% in challenged group	Huff *et al.* (2004)
E. coli	High (1.0×10^9 PFU/ml) and low (5.0×10^7 PFU/ml) titers	Oral inoculation and spray into the beak of broiler chickens	Protection against the bacterium colonization ↓ MR	Oliveira *et al*. (2010)
E. coli	8×10^8 PFU/ml	Spraying of chicken's litter (200 ml/3.9 m^2 surface) of 2-3-week-old broiler chickens	↓ MR and the shedding rate	El-Gohary *et al*. (2014)
C. perfringens	A bacteriophage cocktail contains different phages (10^5 PFU/ml)	Feed and water treatments of broiler chickens	Improvement of weight gain and feed conversion ratio ↓ MR	Miller *et al.* (2010)

CFU: Colony forming units, PFU: Plaque forming units, and MR: Mortality rate (↓ reduced and ↑ increased)

positive (Wysok *et al*., 2015). Moreover, in 2018, the recent report of the European Food Safety Authority (EFSA) and the European Centre for Disease Prevention and Control (ECDC) (2017) indicated that the prevalence rates of *Campylobacter* spp. were 71.6% in turkeys, 26% in broilers, 37.5% in chicken's meat, and in 28.2% turkey's meat (EFSA and CDC, 2017). These bacteria can colonize the chicken's gut at the 7th day post-hatching and the infected chicks may become carriers without exhibiting a disease picture. Both *Campylobacter jejuni* (86.1% or 64.6%) and *C. coli* (13.9% or 35.4%) are the most prevalent types in poultry. There are many reports indicated the emergence of antibiotic resistance against these bacteria, therefore, searching alternatives is urgently needed (Abd El-Ghany *et al*., 2015; Marotta *et al*., 2015; Firlieyanti *et al*., 2016; Nowaczek *et al*., 2019).

Despite the obvious need for implementing novel solutions to reduce the infection rates induced by *Campylobacter* spp., there are no available specific commercial phage products either for commercial poultry or for retail chicken products. Compared with most other lytic phages, *Campylobacter* phages cocktails exhibit some characteristics which make their production and application rather difficult. The production of safe cocktails requires optimization methods for isolation, propagation, and purification of phages. Moreover, although there is no genetic differences among *Campylobacter*-phages, there are differences in the host range, lytic activity, or kinetics which induce difficulties in the selection of appropriate phage candidates for application. The problem of post-phage treatment resistance, besides the cost of production have been also demonstrated (Jäckel *et al*., 2019). The preventive bacteriophages strategy could not prevent *Campylobacter* spp. colonization in some cases

(Carvalho *et al*., 2010).

However, some research work showed evidences for the efficiency of bacteriophages treatments in reducing the *Campylobacter* colonization in broiler chickens and in consequence diminishing the food chain contamination (Table 2). For instance, Atterbury *et al*. (2005) reported a significant reduction in the number of *C. jejuni* ($10^{5.1}$ CFU/g) when compared with the non-treated chickens (10^7 CFU/g). A similar reduction of *C. jejuni* count on chicken carcasses was obtained (Atterbury *et al*., 2003). Oral treatment of chickens with a virulent *C. jejuni* bacteriophage cocktail diminished the bacterial count without effect on the gut microbiota, and therefore reduce human exposure during the consumption of poultry products (Richards *et al*., 2019). Using specific bacteriophages for *C. jejuni* and *C. coli* in the water or feed of broiler chickens induced a significant reduction (2 $\log_{10}$ CFU/g) in the colonization of both bacteria (Carvalho *et al*., 2010).

The resistance of *Campylobacter* spp. to specific bacteriophages could reach to about 4% (Wagenaar *et al*., 2005) and 2% (El-Shibiny *et al*., 2009), therefore, a combination of many specific *Campylobacter* bacteriophages may enhance the bacteriophages efficacy (Johnson *et al*., 2008).

Clostridium spp.

Clostridium perfringens is a natural component of soil, sewers, and drainage water of poultry processing facilities and chickens gut microbiota. The bacterium is a Gram-positive, anaerobic, non-motile, rod-shaped, and spores former. Despite *C. perfringens* is non-pathogenic in poultry, its pathogenicity is related to toxins especially type A and type C. The infections with a toxigenic *C. perfringens* strains produce necrotic enteritis with a significant economic loss in poultry industry. In addition, the presence of enterotoxic strains of *C. perfringens* on chicken's meat is associated with a foodborne disease and human's intoxications (Van Immerseel *et al*., 2004).

Almost all of the produced bacteriophages were unable to infect different strains of *C. perfringens* or with a limited bactericidal activity (Smith, 1959; Seal, 2013). However, certain bacteriophages enzymes such as endolysins and murein hydrolase are regarded as excellence additives for controlling *C. perfringens* infection (Zimmer *et al*., 2002a, b; Nariya *et al*., 2011; Gervasi *et al*., 2014). These enzymes in phages could bind to the peptidoglycans of the Gram-positive bacterial walls and accelerate the destruction lysis of these bacteria. Moreover, Heo *et al*. (2018) evaluated the synergistic effect of combined phages (P4 and A3) and bacteriocin of *Streptococcus hyointestinalis* against *C. perfringens* isolated from chickens and pigs. The results indicated a more significant reduction of bacterial count in a mixed treatment than in a single one. In addition, Miller *et al*. (2010) demonstrated that a bacteriophage treated chickens showed more successful decreasing in mortality than those treated with a formalin-inactivated vaccine containing *C. perfringens*-alpha toxin.

Escherichia coli

E. coli may act as both a primary and secondary pathogen. Avian pathogenic *E. coli* may lead to increasing mortality and condemnation rates in poultry flocks. Moreover, some toxins producing *E. coli* strains are food-borne and cause serious human diseases (Nolan *et al*., 2013).

A recent *in-vitro* study showed that treatment with phage GN06 induced an inhibition of avian pathogenic *E. coli* growth in the liquid medium and in biofilm (Wang *et al*., 2022). Phage flora showed a wider lytic spectrum to inhibit the biofilm formation in *E. coli* culture than kanamycin sulphate (Jiang *et al*., 2022).

Lytic bacteriophages R, originated from human sewage, have crossed the blood-brain barrier and induced a complete reduction of mortalities and meningitis in hens experimentally infected with *E. coli* (Barrow *et al*., 1998). When bacteriophages were given (1-2 days) prior *E. coli* challenge or during the onset of the disease, they could reach early to the brain of infected chicken, rapidly multiply, and reduce the bacterial count, mortality and the course of infection. Therefore, phages may be used in the prevention and early treatment of *E. coli* infection (Barrow *et al*., 1998). Similarly, the early intra air-sacs inoculation of bacteriophage (just after challenge) resulted in absence of the clinical signs and significant reduction of mortality from 50% to 20% (Huff *et al*., 2003). In addition, intramuscular inoculation of bacteriophages significantly decreased the mortality rates from 53% to 17%, 46% to 10%, and 44% to 20% when given immediately, 24 h or 48 h post-challenge, respectively (Huff *et al*., 2003). However, the authors also concluded that the oral application of bacteriophages in the drinking water was ineffective in reducing the severity of signs or controlling of such infection (Huff *et al*., 2003). Moreover, Huff *et al*. (2004) reported that the mortality rate related colibacillosis in challenged and bacteriophage treated 7-day-old chicks was reduced to below 10% in comparison with 60% in non-treated challenged chicks. Combining treatment of hens with bacteriophage and enrofloxacin against *E. coli* infection was effective and could reduce the use of antibiotics in treating bacterial diseases (Huff *et al*., 2004). Nearly similar results were obtained by Xie *et al*. (2005), who demonstrated that oral phage treatment (sewage origin) of 20-day-old chickens induced more reduction of diarrhea and mortality rate produced by entero-pathogenic *E. coli* when compared with chickens received a chloramphenicol antibiotic. The authors also mentioned that used phage was safe, non-toxic, highly specific, and did not adversely affect the beneficial microflora. The intra-tracheal inoculation of chickens with bacteriophags prevented the mortality, reduced the severity of single infection with pathogenic *E. coli* or mixed infection with infectious bronchitis virus, and diminished the bacterium count as well as the virus shedding (Tawakol *et al*., 2019).

Staphylococcus aureus

Staphylococcus spp. including *S. aureus* are normal

inhabitants of skin and mucous membranes of healthy birds and are ubiquitous in the poultry surroundings. Under certain condition, pathogenic strains of *S. aureus* may cause decreased production, mortalities, and carcass condemnation at processing. The clinical pictures of *S. aureus* infections in poultry including arthritis, synovitis, osteomyelitis, chondronecrosis, gangrenous dermatitis, footpad abscesses (bumblefoot), green liver-osteomyelitis complex in turkey, and septicemia (Andreasen, 2013). In humans, some enterotoxin-producing strains of *S. aureus* many contaminate the chicken's carcasses at slaughter causing food poisoning. Moreover, methicillin-resistant *S. aureus* present on carcasses may raise concerns as well (Fessler *et al*., 2011).

Staphylophages are categorized into 3 classes: I-Podoviridae, II-Siphoviridae, and III-Myoviridae (Leskinen *et al*., 2017). Myoviruses and podoviruses are regarded as the most important staphylococcal phages (Leskinen *et al*., 2017). However, phages induced from *S. aureus* strains with chicken and turkey origins are belonging to the family Siphoviridae of the order Caudovirales. Moreover, they are classified into serogroups A, B, and F (Fa and Fb), and have strong lytic properties against *Staphylococcus* spp. and other bacterial strains. Despite bacteriophages are highly specific to *S. aureus*, some harbored enterotoxigenic genes that make them impractical in phage therapy (Marek *et al*., 2019).

Listeria monocytogenes

Listeria monocytogenes is a food-born bacterium that can grow under low temperature conditions. The US Department of Agriculture (USDA) and the U.S. Food and Drug Administration (U.S. FDA) approved the use of a bacteriophage product as a food additive for the ready-to-eat meat and poultry products against *Listeria* spp. contamination (Housby and Mann, 2009). That phage product was a mixture of 6 specific lytic bacteriophages that could be applied directly on food without any adverse effects on the organoleptic quality (Perera *et al*., 2015). Another type of bacteriophage-based product (contains a single phage P100) also showed a strong efficacy against *L. monocytogenes* without any toxic effect. It has been reported that the phages efficacy depends on their initial concentration and the storage temperature (Bigot *et al*., 2011).

Disinfection

Strict biosecurity measures including disinfection are a key role for the prevention of important threats affecting poultry production and human health. Reducing the prevalence of zoonotic pathogens infections at the farm level can reflect the degree of contamination of poultry facilities and meat products. For example, spaying of litter in poultry farms helps in reducing the horizontal transmission of viral and bacterial infections (Gamal *et al*., 2018).

Some phages can be used as suitable disinfectants (Barrow *et al*., 1998). Bio-sanitizers including bacteriophage-based products may be used in poultry production chains as hatcheries, farms, transport crates, processing plants, and food contact surfaces. They can prevent the formation of bacterial biofilms on the surfaces of the facilities and equipment. Garcia *et al*. (2017) used bacteriophages to control *S.* Enteritidis and *S.* Heidelberg biofilms on surfaces of chicken's slaughterhouses. Moreover, they have been applied directly as wash, mist, or spray surface disinfectants on the live animals prior to slaughter to reduce the contamination with important zoonotic bacterial infections such as *Salmonella* spp. Likewise, *E. coli* O157:H7-based phage product has been developed for the skin decontamination of live animals before slaughtering (Sommer *et al*., 2019). Disinfectant bacteriohages could be used on artificially contaminated skin of broiler chickens to reduce the number of *C. jejuni* (Atterbury *et al*., 2003). Also, Hungaro *et al*. (2013) confirmed the efficacy of a biosanitizer that consisted of 5 phages cocktail from chicken feces to reduce *S.* Enteritidis load on the skin of chickens when compared with chemical agents. Moreover, a bacteriophage spray preparation was practical and efficacious for the control of *E. coli* in the litter of broilers farms (El-Gohary *et al*., 2014).

Food preservation

It is known that decontamination or good food preservation resulting in reducing most of zoonotic pathogens affecting humans. Heat pasteurization, high pressure, acids, and radiation are the most common methods of food preservation. However, some methods are not suitable for the preservation of raw meat because they may affect the quality and appearance of the meat. Thus, using bacteriophages for the preservation of food is considered as a safer and a chemical free method than other chemical preservatives. Phages have been used to decrease the contamination of meat products (García *et al*., 2008). Phages can provide a natural biocontrol method for the elimination of bacteria particularly those of zoonotic nature. Prevention of *L. monocytogenes* growth in the food was achieved via the addition of 6 lytic bacteriophages without adverse impact on the organoleptic quality of food (Perera *et al*., 2015). Peracetic acid used in the food industry showed a neutralizing activity against surface bacteriophages (Marco *et al*., 2019). Therefore, the food products can be preserved using phage preparations approved by FDA in USA and European Union (Vikram *et al*., 2021).

Improving performance parameters and immunity

An improvement of the performance parameters of broilers and layers was reported following the administration of dietary bacteriophages to reduce some pathogenic enteric bacterial infection (Adhikari *et al*., 2017; Noor *et al*., 2020). The dietary supplementation of

broiler chickens with bacteriophages could improve the body weight gain, feed conversion ratio (FCR), and European efficiency factor, modulate the gut microbial composition, boost the immune system, improve the intestinal morphology, and increase the concentration of short chain fatty acids (Sarrami *et al*., 2022). Similarly, Kim *et al*. (2013 and 2014) found enhanced body weight gain and FCR by increasing the bacteriophages levels in the broilers' diet. However, Wang *et al*. (2013) demonstrated that supplementation of broilers with bacteriophages had no beneficial effects on the body weight or FCR. In layer chicken flocks, the beneficial effect of using bacteriophages was studied by Zhao *et al*. (2012) and the results indicated that the dietary supplementation with 0.035% and 0.05% of bacteriophages significantly improved the egg production parameters. A similar improvement in the layer's performance has been also reported (Kim *et al*., 2015).

Following oral treatment, bacteriophages colonized the caecum of broiler chickens where the short chain fatty acids are present in high concentrations (Sarrami *et al*., 2022). Short chain fatty acids showed various important functions in the gut. They reduce the gut pH, inhibit the proliferation of some acid-sensitive pathogens such as Enterobacteriaceae, produce energy, stimulate the intestinal epithelial cells proliferation, increase the villus height and surface area, regulate the blood flow, stimulate enterocytes proliferation, and control mucin production (van der Wielen *et al*., 2000; Pan and Yu, 2014; Clavijo and Flórez, 2018; Yadav and Jha, 2019).

In comparison with the antimicrobial feed additives, bacteriophages induce fewer negative changes in the normal gut microbiota which are important to inhibit the secondary pathogenic bacterial infections, provide more important metabolic substrates as vitamins, fatty acids, etc., and better enhance the immune system (Azizian *et al*., 2013; Rubio, 2019). Moreover, bacteriophages can modify the intestinal bacterial populations and gut health, reduce the intestinal inflammation, and improve the differentiation and migration of proliferative cells in the intestinal crypts (Sarrami *et al*., 2022).

The gene expression of a toll-like receptors (*TLR*4) was more deceased, while the transcription of IL-10 was more increased in broiler chickens fed on a diet containing 0.5-1 g bacteriophage/kg diet than colistin treated chickens (Sarrami *et al*., 2022). Bacteriophages naturally act as pathogens killers by reducing the concentration of lipopolysaccharides and consequently the *TLR*4 expression in the intestinal cells. Besides, the most important immune-regulatory effect of IL-10 is the inhibition of the effector functions of the activated phagocytes, T cells, and non-immune cells. Schreiber *et al*. (1995) demonstrated that IL-10 down-regulated the transcription and secretion of some pro-inflammatory cytokines such as IL-1β, IL-6, and IL-8. Thus, it considered as a key factor in maintaining normal non-inflammatory intestinal immune-regulation (Fukushima *et al*., 1993).

Bacteriophages are also able to stimulate the production of specific humoral antibody responses which may influence the phage therapy in humans, animals, and poultry (Huff *et al*., 2010). Bacteriophages can activate the innate immune system by the production of specific neutralizing antibodies (Górski *et al*., 2012) and non-neutralizing immunoglobulins (IgM and IgG) (Capparelli *et al*., 2010; Nilsson, 2014). It has been demonstrated that increasing the level of oral bacteriophages therapy resulting in an increase in the serum concentrations of IgG and IgM, and consequently an increase in the birds' immune response. It may be suggested that antibodies produced against bacteriophages can help in the stimulation and response of the immune system to the other similar virus structures. Generally, bacteriophages can boost the immune system either directly through entering the circulatory system and stimulating the humoral and cellular immunity, or indirectly via their modulatory effects of the gut microflora (Sarrami *et al*., 2022). The increase in the relative weight of thymus glands and bursa of Fabricius in response to dietary inclusion of bacteriophages is an indicator for the enhancement of bird's immune response (Sellaoui *et al*., 2012; Sarrami *et al*., 2022).

Limitations of bacteriophages application

Selection and production

The selection of potential bacteriophages is an important initial step as they should be virulent and able to propagate through the lysogenic or lytic cycle. The sequencing process is important to ensure that bacteriophages will not integrate on the host genome and hence prevent the transduction and horizontal gene transfer (Santos *et al*., 2010). From the economic point of view to meet the poultry markets, the production of large quantities of bacteriophages is a great challenge. Therefore, the most cost-effective method was to use one bioreactor (156 L) for 6 phages, followed by filtration processes using 0.45 µm and 0.22 µm filters to remove biomass and ensure sterility, respectively. Strict regulations during phages preparation, manufacturing, and production should be complied to ensure high safety and standards suitable for their applications. Moreover, the production titer should be optimized and improved to diminish the production costs (Torres-Acosta *et al*., 2021).

Although there are no specific guidelines that could be followed for the production of bacteriophages (Knezevic *et al*., 2021), Regulski *et al*. (2021) developed quality and safety criteria for the bacteriophage therapy product. For example, phages encode lysogeny, virulence genes, or antibiotic-resistant bacteria should not be used to prevent the spread of these factors. In addition, some fastidious bacterium such as *C. difficile* is difficult to be treated with bacteriophages; thus, there are no available phage product (Hargreaves and Clokie, 2014; Mutti and Corsini, 2019). Sometimes, lysing bacteria release endotoxins proteins that cause fever and toxic shock of the host (Krylov *et al*., 1993). Consequently, the phages

should be free from any impurities such as endotoxins and the threshold levels should be established (Pirnay *et al*., 2015). Also, a full characterization or screening of bacteriophages is crucial to exclude the foreign proteins or toxic substances which may potentially provoke the immune responses, reduce the effectiveness of therapy, or cause death with anaphylactic shock (Wright *et al*., 2009).

Delivery to the intestine

It is important to detect the optimal timing and delivery of bacteriophages in the poultry industry setting (Lim *et al*., 2012). Significant numbers or doses of bacteriophages are essential to adsorb individual host cells (Zimmer *et al*., 2002a). The colonization of chicken caecum by *S. enterica* serotypes Enteritidis and Typhimurium was inhibited for only 24 to 48 h following bacteriophage treatment. Certain cases showed that the efficacy of bacteriophages therapy should be exploited by the use of a high titer of bacteriophages such as 10^6 PFU (Barrow *et al*., 1998). Huff *et al*. (2002) found that lower doses of bacteriophages, e.g., 10^2 PFU, induced no statistically significant protection against *E. coli* infection.

The pharmacodynamics and pharmacokinetics of bacteriophages therapy are complex processes (Dąbrowska and Abedon, 2019; Danis-Wlodarczyk *et al*., 2021). The intestinal bacterial cells colonize the gut, therefore, bacteriophages should be delivered into the gastrointestinal tract following their oral administration. However, the most important challenges for oral delivery of bacteriophages are the acidic gastric pH and temperature. Bacteriophages are stable between pH 4-10 (Casey *et al*., 2018) as they should remain viable and withstand the wide pH variations. Thus, a liposome-encapsulated bacteriophage preparation has been found to be more stable in pH 2.8 and 4°C for at least 3 months when compared with free bacteriophages (Colom *et al*., 2015). Outside the host, bacteriophages preparations could be directly applied on carcasses (meat, skin), packaging materials, and processing facilities (Żbikowska *et al*., 2020).

Resistance

There is a possibility for the development of resistance against therapeutic bacteriophages. The mechanisms by which the bacteriophages resistance has been emerged may include alteration of their receptors, blockage of DNA injection, or inhibition of replication. This resistance may lead to a fitness cost for the bacterial cells (Stern and Sorek, 2011). Andreatti Filho *et al*. (2007), found that *S*. Enteritidis colonization was prevented for 48 h after oral treatment with a bacteriophages cocktail which may partly due to the development of acquired resistance to the bacteriophage by the bacteria. However, resistance mutants can be overcome or avoided through the application of bacteriophages cocktails or rotation schedules. In the study of Clavijo *et al*. (2019), the results showed un-expected reduction in *Salmonella* count in broiler chicken flock houses following effective disinfection practices and bacteriophages cocktail rotation program. Moreover, high titers of bacteriophages may reduce the build-up or accumulation of bacteriophage-resistant bacteria particularly after using as post-slaughter disinfectants preparations (Fister *et al*., 2019). Besides, a ratio of bacteriophages to bacterial cells can also help in the limitation of resistance (Labrie *et al*., 2010).

Possibilities of a bacteriophages-antibiotics combination therapy

Some studies have indicated successful combination therapies with bacteriophages and medicine for some human diseases (Torres-Barceló and Hochberg, 2016). Mixed antibiotics and bacteriophages preparations showed synergistic effects in terms of enhanced bacterial suppression and lower bacterial resistance (Tagliaferri *et al*., 2019). The timing and order of bacteriophages with antibiotics should be taken into consideration as it can impact the synergistic activity. *In-vitro* study of Jeon and Ahn (2020), demonstrated that treatment of *S*. Typhimurium infection with a bacteriophage before ceftriaxone and ciprofloxacin addition was more effective in comparison with treatment with bacteriophages 6 h post-antibiotics treatment. Moreover, the existence of antibiotics did not adversely affect the bacteriophages binding activity to *Salmonella* with a significant enhancing of bacteriophages lytic activity (Jeon and Ahn, 2021). This combined approach can lead to re-establishment of antibiotic sensitivity, particularly in cases where bacteriophages combined to bacterial drug efflux pumps (Tagliaferri *et al*., 2019). The *in-vivo* bacteriophages-antibiotic synergy studies are limited in poultry research work. Therefore, further studies are essential to understand the underlying dynamics of this synergy and to help develop useful combinational therapies. This bacteriophage-antibiotic combination is a promising development that needs further research.

Conclusion

Bacteriophage production, delivery and usage, as an effective treatment in commercial production settings, in a cost effective way has yet to be investigated so that scale up of bacteriophage(s) usage as a viable practical alternative to antimicrobials in animal commercial production is proven as a practical solution for different infections.

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Conflict of interest

The authors declare that no conflict of interest could

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