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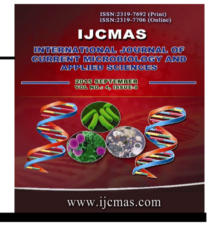


**Review Article**

# Bacteriophages are Alternative Bio Control Agents to Prevent the Food Borne Pathogens

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**A B S T R A C T**

The increased incidence of food borne illness has caused substantial morbidity and mortality worldwide annually, often associated with outbreaks and food contamination. According to Centers for Disease Control and Prevention, food borne illness is known to be a ubiquitous, costly, yet preventable public health concern. Phages can be used to control pathogens in food at all stages of production in the classic "Farm-to-fork" continuum in the human food chain. In pre-harvest control of food borne pathogens, phage therapy can be used to prevent as well as reduce colonization and disease. Phages can also serve as bio control agents or bio sanitizers in the post-harvest control of Food borne pathogens in meat, fresh produce and processed foods. Finally, the use of phages has also been proposed as bio preservatives in the extension of the shelf-life of manufactured foods.

**Keywords**

Bacteriophage, Pseudomonas, Biocontrol, Biosanitizer, Biopreservatives

## Introduction

Food is a fundamental requirement of everyday life (Lorraine Endersen *et al.,* 2014). Everyday people Worldwide buy and consume a diversity of food products of animal and plant origin (Sanna M. Sillankorva *et al.,* 2012). Food is the primary route of transmission for more than 200 known diseases (Lorraine Endersen *et al.,* 2014). Food borne disease are a growing public health problem worldwide Gram-negative bacteria are common inhabitant of the gut of warm-blooded animals, especially livestock, being transmitted to humans primarily through the consumption of contaminated food of animal origin (Lorraine Endersen *et al.,* 2014; Carla M. Carvalho *et al.,* 2012). Food borne disease do not only occur in developing countries, in the united states of America for example, it is estimated that food borne disease result in approximately 76million illnesses 325,000 hospitalization and 5,000 death each year (Lorraine Endersen *et al.,* 2014; Sirsa *et al.,* 2009; Chibeu, 2013).

Statistical data on the worldwide incidence of food borne disease are fragmented, mainly focusing on specific pathogens or their rate of occurrence in particular countries (Lorraine Endersen *et al.,* 2014; Carla M. Carvalho *et al.,* 2012).

As a consequence of this, the true measure of food borne illness on a global scale is unattainable (Lorraine Endersen *et al.*, 2014). In addition to microbial contamination Food products may become contaminated at different stages along the food chain, from growth or production until the final consumption (Sanna M. Sillankorva *et al.*, 2012) posing a threat to health and well-being, it also impacts greatly the food industry in terms of food spoilage (Lorraine Endersen *et al.*, 2014).

Several antimicrobial treatments have been used in the food industry to decontaminate food, destroy disease-causing pathogens, and preserve food (Sirsa *et al.*, 2009) and use of antibiotics has been restricted over the years due to the risk of antibiotic-resistant bacteria entering the human food chain and causing negative impact on human antimicrobial treatment (Chibeu, 2013).

Use of antibiotics as growth promoters in animal production, together with the risk of antibiotic-resistant bacteria entering the human food chain have been the driving force for the development of alternative methods for pathogen control.

Bacteriophages are naturally occurring predators of bacteria, ubiquitous in the environment, with high host specificity and capacity to evolve to overcome bacterial resistance which makes them an appealing option for the control of pathogens (Carla M. Carvalho *et al.*, 2012).

Bacteriophages (phages) have found use as natural antimicrobials that can be used in controlling bacterial pathogens in foods and food processing environments (Chibeu, 2013; Mohamed Elbreki *et al.*, 2014). Phages as bio control agents against food pathogens and food spoilage organisms, highlighting their suitability for use in the food industry.

## Bacteriophage

### History and Biology of Bacteriophage

Bacteriophages (or phages) were discovered in 1915 and 1917 by Frederick Twort and Félix d'Herelle respectively (Masoud Sabouri Ghannad and Avid Mohammadi, 2012; Sanna M. Sillankorva *et al.*, 2013; Zuzanna Drulis-Kawa *et al.*, 2012; Mathur *et al.*, 2003; Stephen T. Abedon *et al.*, 2011; Alexander Sulakvelidze *et al.*, 2001). However, d'Herelle was the first scientist who applied the term "*Bacteriophage*"; a microbe that has the potential to attack bacteria and kill them. He was also the first to report that the agent of bacterial death was in fact a virus (Zhabiz Golkar *et al.*, 2014; Irshad Ul Haq *et al.*, 2012; Hywel TP Williams, 2013).

Phages are the most abundant organisms on earth (Masoud Sabouri Ghannad and Avid Mohammadi, 2012; Zhabiz Golkar *et al.*, 2014; Irshad Ul Haq *et al.*, 2012; Hywel TP Williams, 2013; Céline Verheust *et al.*, 2010) and are ubiquitous in the nature (Céline Verheust *et al.*, 2010; Stan Deresinski, 2009; Jameel M. Inal, 2003; Alexander Sulakvelidze *et al.*, 2001; Masoud Sabouri Ghannad and Avid Mohammadi, 2012; Sanna M. Sillankorva*et al.*, 2013; Zuzanna Drulis-Kawa *et al.*, 2012). More than 5000 classified bacteriophages are known (Masoud Sabouri Ghannad and Avid Mohammadi, 2012; Céline Verheust *et al.*, 2010; Stan Deresinski, 2009). At present, over 5500 different bacteriophages have been discovered, each of which being able to infect one or several types of bacteria generally, phages as obligatory parasites of a bacterial cell show several life cycles: lytic, lysogenic, pseudolysogenic and chronic infections (Zuzanna Drulis-Kawa *et al.*, 2012; Stan Deresinski, 2009).

Bacteriophages, of which there are currently 13 families and 30genera, are believed to be the most abundant life form on the planet, suffusing the biosphere with a predicted $1X10^8$ species (Stan Deresinski, 2009) comprised of an estimated total of $1X10^{30}$ to $1X10^{32}$ phage particles; if gathered, these particles would weigh $1X10^9$ metric tons (Stephen T. Abedon *et al.,* 2011). Phages are ubiquitous, with, for example, an estimated $1X10^6$ particles per drop of seawater and as many as $1X10^8$ particles per g of soil (Zuzanna Drulis-Kawa *et al.,* 2012; Stan Deresinski; 2009). Phages are easily identified in the water sources, sewage soil and even ocean depths (Céline Verheust *et al.,* 2010Stan Deresinski, 2009; Jameel M. Inal, 2003; Mai Huong Ly-Chatain, 2014; Masoud Sabouri Ghannad and Avid Mohammadi, 2012; Zuzanna Drulis-Kawa *et al.,* 2012).

Rapid evolution of phage and their hosts imply that evolutionary dynamics are likely to be a factor in many natural and applied scenarios; thus understanding how phage affect the evolution of host bacteria is of key importance (Hywel TP Williams, 2013). The "virulent" and "temperate" phages differ in their mode of action (Mathur *et al.,* 2003; Stan Deresinski, 2009; Jameel M. Inal, 2003; Mai Huong Ly-Chatain, 2014). The first step of the phage infection is adsorption of the phage particle to the bacterial cell wall by specific interactions between viral surface proteins and host cell receptors. After entering the bacterial cell, the virulent phages replicate rapidly to synthesize genome and structural proteins into progeny virions inside the host cell. Finally the new phages escape by rupturing the cell wall which results in the death of the cell. In contrast, temperate phages integrate their genetic material into the chromosome of the host cell, which is replicated along with the host cell genome (prophage). They can, therefore, subsequently emerge inside a new host cell. Only temperate phages which can enter the bacterial genome participate in horizontal gene transfers between bacterial populations. For antibacterial applications, virulent phages which have the ability to rapidly lyses bacterial cells are employed (Mai Huong Ly-Chatain, 2014; Stan Deresinski, 2009; Jameel M. Inal, 2003; Zuzanna Drulis-Kawa *et al.,* 2012; Mathur *et al.,* 2003).

After the discovery of bacteriophages in early 20th century many researchers thought about their (phages) potential of killing bacteria, which could undoubtedly make them possible therapeutic agents. But after World War II when antibiotics were discovered, this natural potential therapeutic agent got little attention and was only considered as a research tool for many years (Masoud Sabouri Ghannad and Avid Mohammadi, 2012; Irshad Ul Haq *et al.,* 2012; Mai Huong Ly-Chatain, 2014). Bacteriophages have contributed a lot to the field of molecular biology and biotechnology and are still playing its part. Many mysteries of molecular biology are solved by bacteriophages. Today when everything is much more advanced than ever before, bacteriophages are getting enormous amount of attention due to their potential to be used as antibacterials, phage display systems, and vehicles for vaccines delivery.

(Bacterio)phage, viruses are obligate parasites. They are ubiquitous in nature (Marcela Leon and Roberto bastlas, 2015) and form the most numerically abundant biological entities on earth with an estimated population of about 1030 to 1032 phage particles - this makes them key contributors in the regulation of the microbial balance in every ecosystem (Chibeu, 2013) and they specifically infecting bacteria (Steven Hagens and Martin J. Loessner, 2010; Lorraine Endersen *et al.,* 2014) are harmless to humans, animals, and plants. Since the discovery of phages in 1915, they have been extensively used not only in human and veterinary medicine but also in various agricultural settings. Being obligatory parasites, upon multiplication by taking over host protein machinery, phages can either cause cell lysis to release the newly formed virus particles (lytic pathway) or lead to integration of the genetic information into the bacterial chromosome without cell death (lysogenic pathway).Towards a food safety perspective, strictly lytic phages are possibly one of the most harmless antibacterial approaches available (Sanna M. Sillankorva *et al.*, 2012; Stephen T. Abedon *et al.*, 2011; Marcela Leon and Roberto bastlas, 2015; Steven Hagens and Martin J. Loessner, 2010; Andrew G Lum *et al.*, 2015).

## Phage therapy & its advantages

Phages offer advantages as bio control agents for several reasons: (i) high specificity to target their host determined by bacterial cell wall receptors, leaving untouched the remaining microbiota, a property that favors phages over other antimicrobials that can cause microbiota collateral damage; (ii) self-replication and self-limiting, meaning that low or single dosages will multiply as long as there is still a host threshold present, multiplying their overall antimicrobial impact; (iii) as bacteria develop phage defense mechanisms for their survival, phages continuously adapt to these altered host systems; (iv) low inherent toxicity, since they consist mostly of nucleic acids and proteins; (v) phages are relatively cheap and easy to isolate and propagate but may become time consuming when considering the development of a highly virulent, broad-spectrum, and non transducing phage; (vi) they can generally withstand food processing environmental stresses (including food physiochemical conditions); (vii)they have proved to have prolonged shelf life (Lorraine Endersen *et al.*, 2014; Céline Verheust *et al.*, 2010; Lawrence D. Goodridge and Bledar Bisha *et al.*, 2011; Andrew M Kropinski *et al.*, 2012; Aan Loh Teng-Hern *et al.*, 2014).

Phages are readily abundant in foods and have been isolated from a wide variety of raw products (e.g., beef, chicken), processed food (e.g., pies, biscuit dough, and roast turkey), fermented products (e.g., cheese, yoghurt), and seafood (e.g., mussels and oysters). This suggests that phages can be found in the same environments where their bacterial host(s) inhabit, or once were present and that phages are daily consumed by humans (Lorraine Endersen *et al.*, 2014; Céline Verheust *et al.*, 2010; Lawrence D. Goodridge and Bledar Bisha *et al.*, 2011; Andrew M Kropinski *et al.*, 2012; Aan Loh Teng-Hern *et al.*, 2014).

## Phages targeting different food pathogens

The global incidence of foodborne disease and costs associated are difficult to estimate, however cost at least $7 billion dollars each year in medical expenses and lost productivity in the United States according to the United States Department of Agriculture's Economic Research Service. The actual figure is higher since this estimate reflects illnesses caused only by the major food borne pathogens (Sanna M. Sillankorva *et al.*, 2012).

## Food borne pathogens from animal origin

The four main food borne pathogens from animal origin are accounted to be *E. coli*, *Campylobacter*, *Salmonella*, and *Listeria* (Sanna M. Sillankorva *et al.*, 2012; Chibeu, 2013; Sirsa *et al.*, 2009). These bacteria are all common contaminants of ruminants, poultry, and swine and are usually carried in their gastrointestinal tract asymptomatically. Research on the use of phages against foodborne pathogens from animal origin has mainly focused on the optimization of preharvest interventions where the phage administration routes and delivery processes have received most attention and also on the optimization of postharvest strategies (Sanna M. Sillankorva *et al.,* 2012;). The usage of phages as a preharvest strategy is made directly by administering phages to livestock to prevent animal illness and/or also to minimize the pathogen carriage in the gastrointestinal tract, thereby preventing pathogen entry to the food supply. Postharvest strategies are based on the use of phages directly on animal carcasses in an attempt to sanitize the products (Sanna M. Sillankorva *et al.,* 2012; Chibeu, 2013).

## Phage biocontrol of food-borne pathogens

### *Escherichia coli*

*Escherichia coli* are a gram-negative bacterium. Serotype O15:H7 in particular (Chibeu, 2013; Sirsa *et al.,* 2009; Lorraine Endersen *et al.,* 2014; Aan Loh Teng-Hern *et al.,* 2014) classified as Shiga toxin-producing *E. coli*, is a well-known food poisoning pathogen (Carla M. Carvalho *et al.,* 2012;). Its major reservoir comprises ruminants and, as it can survive well under intestinal conditions (Carla M. Carvalho *et al.,* 2012; Chibeu, 2013). If proper care is not taken during slaughter, the contents of the intestines, fecal material, or dust on the hide may contaminate meats (Lorraine Endersen *et al.*, 2014; Sanna M. Sillankorva *et al.,* 2012; Andrew M Kropinski *et al.,* 2012; Aan Loh Teng-Hern *et al.,* 2014; Lawrence D. Goodridge and Bledar Bisha, 2011). The most common route of *E. coli* transmission to humans is via Under-cooked contaminated food, while water and raw milk are assumed to be related to cross contamination events, by direct or indirect contact with feces (Andrew M Kropinski *et al.,* 2012; Aan Loh Teng-Hern *et al.*, 2014; Chibeu, 2013; Lorraine Endersen *et al.,* 2014; Sanna M. Sillankorva *et al.,* 2012; Carla M. Carvalho *et al.,* 2012). This microorganism is highly virulent and a public health threat because ingestion of a concentration as low as 10 cells is able to cause infection (Lorraine Endersen *et al.,* 2014; Sanna M. Sillankorva *et al.,* 2012; Lawrence D. Goodridge and Bledar Bisha, 2011; Andrew M Kropinski *et al.,* 2012; Aan Loh Teng-Hern *et al.,* 2014).

Phages may be used as biocontrol agents against infection by *E. coli* O157:H7 which typically occurs through ingestion of contaminated food or water, through direct contact with animals, or via person-to-person transmission (Sirsa *et al.,* 2009; Andrew M Kropinski *et al.,* 2012; Aan Loh Teng-Hern *et al.*, 2014). Comparing oral and rectal administration of *E. coli* O157:H7-specific phage cocktail to steers found that oral treatment with the phages was more effective than rectal and rectal-oral administered phage for controlling the fecal shedding of the bacteria (Lorraine Endersen *et al.,* 2014; Sanna M. Sillankorva *et al.,* 2012; Sirsa *et al.,* 2009; Chibeu, 2013; Andrew M Kropinski *et al.,* 2012; Aan Loh Teng-Hern *et al.,* 2014; Carla M. Carvalho *et al.,* 2012; Lawrence D. Goodridge and Bledar Bisha, 2011).

### *Salmonella*

*Salmonella,* is a genus of gram-negative facultative intracellular species, is considered to be one of the principal causes of zoonotic diseases reported worldwide (Lorraine Endersen *et al.,* 2014; Sanna M. Sillankorva *et al.,* 2012; Sirsa *et al.,* 2009; Chibeu, 2013; Andrew M Kropinski *et al.,* 2012; Aan Loh Teng-Hern *et al.,* 2014). This is because they can colonise a wide range of hosts including all major livestock species, eventually producing contaminated meat and other food products. In the USA, more than 50% of salmonellosis is caused by only three *Salmonella enterica* serovars; *Salmonella* Typhimurium, *Salmonella* Enteritidis and *Salmonella* Newport (Chibeu, 2013; Sirsa *et al.*, 2009; Lorraine Endersen *et al.*, 2014). *Salmonella* Typhimurium causes nontyphoid salmonellosis, a disease characterized by abdominal pain, nausea, diarrhea and even life threatening infections. About 40,000 cases of non-typhoid salmonellosis per year are reported in the USA. An increase in salmonellosis in the developed world has been due to *Salmonella* Enteritidis, which is linked to eggs and poultry (Chibeu, 2013; Andrew M Kropinski *et al.*, 2012; Aan Loh Teng-Hern *et al.*, 2014).

*Salmonella* is also a known spoilage bacterium in processed foods (Lawrence D. Goodridge and Bledar Bisha). Once ingested, this microorganism can cause fever, diarrhea, abdominal cramps, and even life-threatening infections (Lawrence D. Goodridge and Bledar Bisha; Andrew M Kropinski *et al.*, 2012; Aan Loh Teng-Hern *et al.*, 2014). To prevent such infections, a number of studies on animal phage therapy have been reported where phages were used to prevent or reduce colonization and diseases in livestock (Sanna M. Sillankorva *et al.*, 2012).

Phages to reduce *Salmonella* Enteritidis colonization in chicken, a cocktail of three phages (BP1, BP2, and BP3) was administered by either coarse spray or in drinking water prior to *Salmonella* Enteritidis challenge. Phage delivery both by coarse spray and drinking water reduced the intestinal *Salmonella* Enteritidis colonization (Chibeu, 2013; Sirsa *et al.*, 2009; Andrew M Kropinski *et al.*, 2012; Aan Loh Teng-Hern *et al.*, 2014).

### *Campylobacter*

*Campylobacter* is a genus of gram-negative, spiral, motile, and microaerophilic bacteria (Sanna M. Sillankorva *et al.*, 2012; Andrew M Kropinski *et al.*, 2012; Aan Loh Teng-Hern *et al.*, 2014; Sirsa *et al.*, 2009; Chibeu, 2013) with an optimal growth temperature around 41°C. *C. jejuni* and *C. coli* members are considered to be major aetiological agents of enteric diseases worldwide. *Campylobacter* is the most commonly reported zoonosis in Europe (EFSA 2011), and *C. jejuni*, in particular, is estimated to cause approximately 845,000 illnesses, 8,400 hospitalizations, and 76 deaths each year in the USA. This widespread infection is explained because ingestion of low doses (400–500 cells) can cause campylobacteriosis typically characterized by fever, bloody diarrhea, and acute abdominal pain. *Campylobacter* is capable of colonizing the intestine of poultry and cattle, and thus infection is mostly acquired by fecal-oral contact, ingestion of contaminated foods (i.e., raw meat and milk contaminated through feces), and waterborne through contaminated drinking water. The widespread disease and economic impact on agriculture and food industries has led to the development of various approaches to contain this infection using bacteriophages (Sanna M. Sillankorva *et al.*, 2012; Chibeu, 2013; Sirsa *et al.*, 2009; Andrew M Kropinski *et al.*, 2012; Aan Loh Teng-Hern *et al.*, 2014).

Phage preharvest interventions reported so far have been successful in reducing *Campylobacter* numbers in the cecal content and feces of experimentally infected broilers and have not caused any adverse health effects (Sanna M. Sillankorva *et al.*, 2012; Chibeu, 2013; Lawrence D. Goodridge and Bledar Bisha, 2011; Andrew M Kropinski *et al.*, 2012; Aan Loh Teng-Hern *et al.*, 2014).

### *Listeria monocytogenes*

*Listeria monocytogenes* is an opportunistic pathogen that has become a major foodborne pathogen of public health concern with a high mortality rate in at risk individuals such as pregnant women, neonates, immunocompromised individuals and the elderly (Sirsa *et al.*, 2009; Chibeu, 2013; Andrew M Kropinski *et al.*, 2012; Aan Loh Teng-Hern *et al.*, 2014). *Listeria monocytogenes* is a gram-positive, motile, and facultative intracellular bacterium, that can grow under several food matrices and storing conditions (e.g., high salt levels, low pH, lack of oxygen, and low temperatures) (Sanna M. Sillankorva *et al.*, 2012; Sirsa *et al.*, 2009; Chibeu, 2013; Andrew M Kropinski *et al.*, 2012; Aan Loh Teng-Hern *et al.*, 2014).

Invasive infection by *L. monocytogenes* causes listeriosis and is transmitted to humans with 103 CFU/mL levels. It is often associated with contaminated minimally processed food such as ready-to-eat (RTE) products, poultry, and dairy products or related to cross-contamination after the heat treatment process of foods stored at low temperatures (Sanna M. Sillankorva *et al.*, 2012; Andrew M Kropinski *et al.*, 2012). This bacterium has the ability to grow at a wide range of temperatures (0.4°C to 45°C) and pH values (4 to 9.6) enabling it to persist within food processing environments for long periods (Chibeu, 2013).

Phage biocontrol should therefore be optimized separately for each food matrices under study. Four other studies have used phage P100, which was highly effective in inhibiting *Listeria* growth at storage temperatures for several days (Sanna M. Sillankorva *et al.*, 2012; Andrew M Kropinski *et al.*, 2012; Aan Loh Teng-Hern *et al.*, 2014).

### *Pseudomonas* spp.

*Pseudomonas* spp. are ubiquitous environmental bacteria commonly found in soil and water and on the surface of fruits and vegetables and are the major pathogens that spoil foods stored aerobically under refrigerated conditions. Milk is commonly spoiled by *Pseudomonas* spp. via post pasteurization contamination or by the production of heat-stable lipases and proteases before pasteurization. *Pseudomonas*-derived proteases and lipases can lead to degradation of milk protein and fat, resulting in bitterness, gelation, and rancidity. The most common species of *Pseudomonas* that causes milk spoilage is *Pseudomonas fluorescens* (Raquel Lo *et al.*, 2015).

Phages have also been applied to control the growth of pathogens in a variety of refrigerated foods such as fruit, dairy products, poultry, and red meats. Phage control of spoilage bacteria e.g., *Pseudomonas* spp. in raw chilled meats can result in a significant extension of storage life. Phage bio control strategies for food preservation have the advantages of being self-perpetuating, highly discriminatory, natural, and cost-effective. Some of the drawbacks of bio preservation with phages are a limited host range, the requirement for threshold numbers of the bacterial targets, phage-resistant mutants, and the potential for the transduction of undesirable characteristics from one bacterial strain to another.

The emergence of multidrug-resistant bacteria has opened a second window for phage as bio control. The increasing number of phage application studies, both by research groups and commercial enterprises, have altogether provided convincing evidence that phages can play an important role in biocontrol of pathogens in food and feed. The direct application of phages to target specific pathogens in or on foodstuffs is a very straightforward approach. Spontaneously occurring phage-resistant mutants are not likely to significantly influence treatment efficacy. Complex phage resistance mechanisms common in bacteria can be pre-empted when screening for susceptibility of large strain collections, and supplemented by continued screening. The use of strictly virulent phages, unable to perform transduction, and devoid of any virulence or pathogenicity associated genes will ensure that problems concerning bacteriophage safety will not be an issue. As a more general rule, a sufficient concentration of infectious phage particles will have to be applied on foods. Last but not least, an important practical challenge is the incorporation of phage application step at the best possible time point into existing processing and production schemes. While phages can obviously help to reduce pathogen loads in foodstuffs, not only scientific considerations will determine the success of different possible applications. For certain applications, long-term plans for avoiding resistance-associated problems will have to be made in advance. Considering the likely situation that phage products will require inclusion of new phages featuring different host ranges at more or less frequent intervals in order to react to changes in the bacterial flora, transparent and quick approval procedures by regulatory authorities would be beneficial.

Using phage therapy for reduce the presence of food borne pathogens in food producing animals and in fresh and processed foods. Phage efficacy under different environmental conditions and physiological conditions of food producing animals, and address the issue of phage resistance. Phage treatments to reduce bacterial pathogens in foods have been clearly demonstrated, and it is likely that more phage products will be developed and used to reduce contamination during food production. Phages can be used as alternative, but also as substitutes of antibiotics and chemical antibacterials, in the control of food borne pathogens in livestock and foodstuff.

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