The Use of Bacteriophages in Animal Health and Food Protection

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1 Introduction

The therapeutic use of bacteriophages, called phage therapy, is most often considered in the light of human medicine. However, application of bacteriophages in veterinary medicine is also important, and in fact, this method is perhaps better developed there than in human medicine. Regulations on the use of bacteriophages to treat animals are less restrictive relative to those on their medical use; thus, it is easier to test efficacy and mechanisms of phage therapy in infections of animals and humans. This chapter is focused on development of phage therapy for animals, including animal breeding, aviculture, and aquaculture. Moreover, the use of phages in food protection will also be discussed briefly, as will be methods for phage isolation, propagation, purification, and administration.

2 Phage Therapy in Animals

During the recent years, the whole world is facing the problem of infectious diseases related to animals that pose a risk to human and animal health (Gupta et al. 2017). This could be caused by various factors, in particular such as rapidly increasing

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emergence of antibiotic-resistant bacteria worldwide (Bengtsson and Greko 2014; Ventola 2015; Carvalho et al. 2017). With the development of agriculture, resistance to antibiotics spread quickly because their overuse and misuse allow the selection of antibiotic-resistant bacteria (WHO 2014; Ventola 2015). Furthermore, the use of antibiotics as a preventative measure has become increasingly common. What is particularly worrying is that in some countries, farmers add antibiotics to animal feed in order to enhance animal productivity and quality of meat. The European Union and several other developed countries have implemented policies to reduce the use of antibiotics, recognizing its role in the rise of antibiotic resistance. Since 2006, the use of antibiotics as growth promoters in animal feeds is forbidden in the European Union (Wegener 2003; Castanon 2007; EU regulation No 470/2009; Millet and Maertens 2011). However, the problem of bacterial infections is not restricted to animal breeding. It is found also in aviculture and aquaculture. This problem, and the possibility to solve it by the use of bacteriophages that are therapeutic agents, is discussed in subsequent sections.

2.1 Animal Breeding

In this subsection, we focused on animal breeding and more specifically on animal husbandry. This chapter shows the current state of knowledge about phage therapy in livestock: cattle (dairy cattle and beef cattle), swine, sheep, and horses.

2.1.1 Phage Therapy in Farm Animals: Overview

Infectious diseases of farm animals are a major global threat to public health, animal health, and welfare (Tomley and Shirley 2009). For this reason, researchers focused on reaching for a new approach in combating bacterial infections. Recent studies indicated that bacteriophages are becoming increasingly attractive for antibacterial therapy, especially for treating various infectious diseases of farm animals and controlling foodborne pathogens (Kazi and Annapure 2016; Lin et al. 2017). Advantages of phage therapy over the use of antibiotics can be their ubiquitous nature, specificity, prevalence in the biosphere, replication at the site of infection, and low inherent toxicity of phages, which makes them a safe technology to control animal diseases (Loc-Carillo and Abedon 2011; Colavecchio and Goodridge 2017). Therefore, phages are being considered valuable antibacterial means, and they give the opportunity to reduce the current use of antibiotics in agriculture, increasing animal productivity, improving their health, and providing environmental protection (Carvalho et al. 2017; Svircev et al. 2018).

2.1.2 Phage Therapy in Cattle

Bovine Mastitis

Bovine mastitis is a common disease and one of the most relevant bovine pathologies. Indeed, according to the data available, it is the most costly disease in the global dairy industry, due to losses (a reduction of output due to mastitis) and expenses (related to

infection prevention) (Hogeveen et al. 2011; Fan et al. 2016; Gomes et al. 2016). For example, in the USA, total loss amount is estimated to be 2 billion dollars per year which gives 140–280 dollars per cow (Sordillo and Streicher 2002). Recent research that took place recently in Sweden showed that the loss caused by one case of mastitis clinica was estimated at US$735 (Hultgren and Svensson 2009). There are numerous etiological factors associated with bovine mastitis clinica. About 137 microbial species, subspecies, and serovars are isolated from the bovine mammary gland (Watts 1988; Sharif et al. 2009). The most important pathogens causing contagious mastitis in cattle are *Staphylococcus aureus* (Gill et al. 2006a; Boss et al. 2016), *Escherichia coli*, and *Streptococcus uberis* (Bradley 2002; Barrett et al. 2005). The abovementioned problem of antibiotic resistance has resulted in dramatic situation that many commonly used antibiotics are ineffective. Therefore phage therapy seems to be a promising alternative. In recent years, researchers tried numerous attempts to control bovine mastitis clinica using phages (Schmelcher et al. 2015; Fan et al. 2016; Porter et al. 2016).

Mastitis Caused by *Staphylococcus*

As mentioned earlier, *Staphylococcus aureus* is one of the most important pathogens causing mastitis (Boss et al. 2016). Bovine mastitis caused by *S. aureus* is especially difficult to fight due to its resistance to antibiotic treatment and its propensity to recur chronically (Gill et al. 2006a). The emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) infection in dairy animals is especially dangerous (Wang et al. 2015). *S. aureus* also shows high resistance against penicillin, tetracycline, ampicillin, and amoxicillin (Jamali et al. 2014; Szweda et al. 2014).

Some studies have demonstrated two different approaches to investigate the efficacy of phages in treatment of *Staphylococcus aureus* infection (Fan et al. 2016). In the first approach, their results indicated that bacteriophage IME-SA1 could eliminate or reduce the level of *S. aureus* and, thus, had a potential to its use in treatment of infections caused by this bacterium. In this research, a group of 100 *S. aureus* strains isolated from swine, poultry, and cows were tested (including MRSA strains). Phage IME-SA1, reported by Fan et al. (2016), displayed lytic activity against 35% of the *S. aureus* isolates. The second approach in the course of their research was to clone and express recombinant phage endolysin Trx-SA1 from this phage. Such recombinant endolysin displayed lytic activity against 43% of the *S. aureus* isolates. In the next step, they used recombinant endolysin Trx-SA1 to treat mastitis. Research has been carried out on four dairy cows with mild clinical mastitis. Each udder quarter was treated with endolysin (intramammary infusion of 20 mg of recombinant endolysin per day). They determined that three udders were infected with *Staphylococcus aureus*, one by *Escherichia coli*, and one by *Streptococcus agalactiae*. During this experiment, they observed changes of pathogens' levels and somatic cells' count in milk samples after treatment of bovine mastitis (samples are taken for 3 days). The experiment performed in this study demonstrated reductions in pathogen levels and somatic cell count (SCC) in milk from the udder quarters with *S. aureus* mastitis, while *E. coli* infection was not treated successfully. Experiments performed by Fan et al. (2016) indicate that phage IME-SA1 and

recombinant endolysin Trx-SA1 might be an alternative treatment strategy for mastitis caused by *S. aureus*.

In another study, performed by Gill et al. (2006a), the efficacy of phages in treatment of established bovine *S. aureus* intramammary infection has been determined. In this experiment, 24 infected cows were treated for a 5-day course with 10-ml intramammary infusions with lytic *S. aureus* bacteriophage K (1.25×10^{10} PFU/ml) or saline as a negative control. These results showed that phage treatment was able to induce a heightened immune response as exhibited by an increase in the SCC of treated udders. On the other hand, the cure rate was 3 of 18 quarters (16.7%) in the phage-treated group, which was not observed in any control samples (Gill et al. 2006a; Basdew and Laing 2011). Summarizing this work, although the phage-treated group was not significantly improved compared with the control group, obtained results are promising. Another study performed by the same group showed that there are several limiting factors in mastitis phage therapy. The main problem is whey protein binding to the bacterial surface, disturbing phage attachment, so phage administration requires further studies and optimization before use (Gill et al. 2006a, b; O'Flaherty et al. 2009; Fan et al. 2016).

Mastitis Caused by *Streptococcus*

Streptococci belong to the most frequently isolated bacterial species from mastitis cases in cow (Keefe 1997; Bradley 2002). Among the streptococci that cause mastitis, there are *Streptococcus uberis*, *Streptococcus agalactiae*, and *Streptococcus dysgalactiae* (Calvinho et al. 1998; Lammers et al. 2001; Notcovich et al. 2016). Studies indicated that the main causes of mastitis in dairy cows were *S. agalactiae* and *S. dysgalactiae*. Recent work, however, indicated that another bacterial species, *S. uberis*, shows up with increasing frequency in mastitis infections (Barrett et al. 2005; Petersson-Wolfe and Currin 2012; Collado et al. 2016; Notcovich et al. 2016).

Endolysins of phages λSA2 and B30 were reported by Schmelcher et al. (2015). In this work, they evaluated therapeutic potential of two lysins against mastitis caused by streptococci. Endolysin activity was tested in milk using commercial whole-fat ultra-high-temperature (UHT) sterilized milk. Samples of milk were infected by *S. dysgalactiae*, *S agalactiae*, or *S. uberis*. In the next step, purified enzyme was added, and samples were taken immediately before and immediately after the addition, as well as 1, 2, and 3 h after infection. In this work, they demonstrated activities of B30 and λSA2 lysins in cow milk against representative strains from the three most relevant mastitis-causing streptococcal species. They observed that λSA2 lysin was characterized by its high activity in milk against *Streptococcus dysgalactiae* (reduction of CFU/ml by 3.5 log units at 100 μg/ml), *Streptococcus uberis* (4 log), and *Streptococcus agalactiae* (2 log), whereas the B30 lysin was less effective. In summary, the B30 lysine exhibited significantly lower activity than λSA2 against all tested species (Schmelcher et al. 2015). Analyzing the results for λSA2, the next step should be experiments with cows.

Mastitis Caused by *Escherichia coli*

Strains of *Escherichia coli* belonging to environmental pathogens commonly cause bovine mastitis. Inflammation of the mammary gland caused by *E. coli* and coliform bacteria is named "coli mastitis," and it is a common and often fatal disease in lactating dairy cows (Hogan and Smith 2003; Malinowski and Gajewski 2009; Hagiwara et al. 2014). According to the available data, only two antibacterial agents have beneficial impacts in the treatment of *E. coli* mastitis. These are fluoroquinolones and cephalosporins. They belong to very important medicines whose use in animals should be heavily restricted and based on bacteriological diagnosis (Suojala et al. 2013). Therefore, it seems necessary to look for new ways to treat mastitis caused by *E. coli*, for example, phage therapy.

Suojala et al. (2013) conducted a study in which they focused on potential use of bacteriophages in preventing *Escherichia coli* mastitis on dairies. They used one phage cocktail consisting of four bacteriophages and tested it on strains from two distinct geographical regions (*E. coli* isolates from dairy cows in Washington State and from New York State). The use of phage cocktail inhibited growth of 58% of the Washington State isolates and 54% of isolates from New York State. These results show that test cocktail had a relatively wide spectrum of action against strains from two distinct regions. These tests were performed on samples of raw milk. They also performed an experiment involving the use of cocktails and bovine mammary epithelial cells. The experiments showed that pretreatment of cell cultures with the phage cocktail substantially reduced adhesion and survival of *E. coli* compared with controls (Suojala et al. 2013).

Bovine Diarrhea

Diarrhea is a commonly occurring disease in calves that causes major losses in dairy animal husbandry because of high calf mortality and morbidity (Anand et al. 2015). According to the report of the 2007 National Animal Health Monitoring System for US dairy, half of the deaths among calves was caused by diarrhea. This is the main reason of productivity and economic loss to cattle producers throughout the world (Cho and Yoon 2014; Muktar et al. 2015). The data shows that enterotoxigenic *E. coli* (in particular *Escherichia coli* ETEC K99+) belongs to the most common reasons that cause diarrhea in beef and dairy calves in a few days after birth (Moxley and Smith 2010; Anand et al. 2016). In 2006, in Norway, losses were estimated to be about US$10 million (where calf production is 284,000 heads per year).

Anand et al. (2016) isolated and characterized a new bacteriophage VTCCBPA9 with a broad host spectrum which showed bactericidal activity against calf diarrheal isolates of *Escherichia coli* in vitro. In this study, they used *Escherichia coli* ETEC isolated from diarrheal bovine calves and determined biological activity of the bacteriophage VTCCBPA9 against these pathogens. The results indicated that bacteriophage VTCCBPA9 showed bactericidal activity against 47.3% (62/131) *E. coli* isolates (also ETEC strains). Most importantly, promising activity effect against ETEC pathogens suggested the use of this virus in phage therapy as a tool against resistant pathogens.

In other studies, performed by Smith and Huggins (1983), it was also shown that phages can be effectively used in treating experimental *Escherichia coli* diarrhea in calves. They tested a cocktail of two bacteriophages B44/1 and B44/2 against *E. coli* B44 (enteropathogenic *Escherichia coli* O9:K30,99)-caused diarrhea. Calves treated by phage mixture had much lower numbers of *E. coli* B44 in their alimentary tract than untreated calves.

E. coli O157:H7 Infection

Escherichia coli O157:H7 is a meaningful human pathogen that resides in healthy cattle and other ruminants and is not a pathogen in these animals (Jeong et al. 2011). Dairy cattle have been identified as the main reservoir of *E. coli* O157:H7 (Wang et al. 1996). Transmission to humans occurs most frequently through eating raw or undercooked beef or drinking raw milk or water while less frequently through contact with manure or animals (Johnson et al. 2008; Ferens and Hovde 2011). Infection with *E. coli* O157:H7 can cause bloody diarrhea, hemorrhagic colitis, hemolytic uremic syndrome (HUS), thrombocytopenic purpura, and death (Griffin and Tauxe 1991). Phage therapy can be a good way to control infections in livestock and can help in protection of people against *E. coli* O157:H7 infection.

Niu et al. (2008) tested 4 bacteriophages against 422 STEC O157:H7 isolates (297 bovine; 125 human). They determined the host range and lytic capabilities of phages rV5, wV7, wV8, and wV11 against a collection of STEC O157:H7 in an in vitro experiment. Phage wV7 lysed all human and bovine isolates, phage rV5 lysed 342 isolates, wV11 lysed 321 isolates, and wV8 lysed 407 of the 422 isolates. These results indicate that tested bacteriophages have the ability to lyse all human and bovine isolates but each of them has a different host range. Analyzing these results, it is recommended to make a phage cocktail and next to try to use it in efficacious on-farm therapy (Niu et al. 2008).

Promising results are demonstrated by Waddell et al. (2000). Their experiment showed successful elimination of *E. coli* O157:H7 in experimentally inoculated (10^9 CFU) calves through the oral administration of 10^{11} PFU of a cocktail of six phages on days −7, −6, −1, 0, and 1 post-inoculation with pathogenic *E. coli* O157:H7 (phage cocktail was added to the milk). The results indicated that the use of multiple doses of phage cocktail is very important in effective phage therapy (Waddell et al. 2000; Zhang et al. 2015a, b).

2.1.3 Phage Therapy in Sheep

Phage therapy in sheep focuses mainly on treatment of infections caused by *E. coli* O157:H7. Interesting results were observed in the work presented by Raya et al. (2006). These researchers have isolated and characterized a new bacteriophage CEV1, efficiently infecting *E. coli* O157:H7. In vitro experiments showed that bacteriophage CEV1 is able to efficiently infect 90% (17/19) of tested *E. coli* O157:H7 strains. In the next step, they focused on in vivo experiments. Studies involved eight sheep (four treated and four control). Tested sheep were inoculated with $\sim 10^9$ CFU/sheep of novobiocin-resistant *E. coli* O157:H7 EDL 933. Then, after 3 days, half of the tested group received either a single oral dose of CEV1

($\sim 10^{11}$ PFU). In order to take samples, after 2 days, animals were humanely euthanized. It was observed that the level of O157:H7 was reduced 2–3 log units in the ceca and rectums of CEV1-treated sheep compared to control. These promising results suggest that treatment with CEV1 may be important element in an approach for reduction of *E. coli* O157:H7 levels in animals (Raya et al. 2006).

In another study performed by the same group, sheep were infected with *E. coli* O157:H7 and treated with a cocktail of two phages, CEV1 and CEV2. In this experiment, three groups of sheep were employed, each group containing four animals. Eight sheep were free of *E. coli* O157:H7-infecting phage and were divided into two groups (1 and 2). The last group (3) contained sheep that were natural carriers of phage CEV. Their data showed that a cocktail of two phages (CEV2 and CEV1) was more effective (>99.9% reduction) than the use of only CEV1 (~99%) compared to the control (group of sheep untreated and free of *E. coli* O157:H7-infecting phage). According to these results, it seems to be a better solution to use phage cocktail in phage therapy for farm animals instead of one single phage. Interestingly, they have also observed that sheep naturally carrying CEV2 and untreated by phage cocktail had the lowest level of tested pathogens (~99.99% reduction) (Raya et al. 2006, 2011).

2.1.4 Phage Therapy in Pigs

Pig Diarrhea

One of the first studies on the efficacy of phages in treatment of piglet diarrhea was demonstrated by Smith and Huggins (1983). They investigated the efficacy of a two-phage mixture (B44/1 and B44/2) against infection induced by enteropathogenic strain of *Escherichia coli* O9:K30,99, called B44, in neonatal pigs. In this experiment, 14 piglets were used which were inoculated orally about 6 h after birth. At a predetermined time after infection, piglet was given 10^{10} PFU of P433 phage by inoculation. Half of the tested pigs were treated by cocktail of two phages at the onset of diarrhea, 13–16 h after infection. None of the treated pigs died, and if there was diarrhea, it was mild. Another half remained untreated, and in those pigs, severe diarrhea developed (four died after 26–65 h). In an in vitro experiment, both phages showed a high capacity to lyse bacteria. A mixture of two phages, P433/1 and P433/2, and phage P433/1 alone cured diarrhea, caused in piglets by strain of *E. coli* P433 (Smith and Huggins 1983; Johnson et al. 2008; Zhang et al. 2015b).

Escherichia coli causing postweaning diarrhea (PWD) is an important cause of death in weaned pigs and occurs widely throughout the world (Fairbrother et al. 2005). PWD is considered a very serious disease affecting pigs during the first 2 weeks after weaning. This disease is revealed by severe diarrhea, dehydration, growth retardation in surviving piglets, and even death. PWD is responsible for economic losses due to mortality, morbidity, and costs of treatment (Rhouma et al. 2017). Colonization factors (CFs) and enterotoxins differentiate ETEC from other categories of diarrheagenic *E. coli*. The main factors of colonization are fimbriae; in the case of pigs, the most frequently encountered fimbrial adhesins are F4 (Dubreuil 2017). Experiments performed by Jamalludeen et al. (2007) focused on phages that

might be used in prevention and treatment of porcine postweaning diarrhea due to O149 enterotoxigenic *E. coli* (ETEC). In their research, they focused mainly on O149:H10:F4, because this is the dominant ETEC serotype. They isolated and characterized nine phages against ETEC. Six of these phages (GJ1–GJ6) lysed O149:H10:F4 ETEC, and their effectiveness was 99–100% of 85 O149:H10:F4 ETEC strains, and three phages (GJ7–GJ9) lysed O149:H43:F4 ETEC with efficiency reaching 86–98% of 42 O149:H43 ETEC strains. These results provide a basis for the use of these bacteriophages in therapy of O149 ETEC infections in weaned pigs (Jamalludeen et al. 2007; Johnson et al. 2008). In another study, also performed by Jamalludeen et al. (2009), they used previously isolated bacteriophages for prophylaxis and treatment of experimental infection of pigs caused by O149:H10:F4 enterotoxigenic *Escherichia coli* (Johnson et al. 2008; Jamalludeen et al. 2009). In this experiment, phages were administered orally shortly after the challenge, and for therapeutic use, they were given 24 h after the challenge, following the onset of diarrhea. During tests, they focused their attention on several parameters: weight change, duration of diarrhea, and severity of diarrhea. Generally, this work indicated that the isolated phages were effective in moderating the course of experimental O149:H10:F4 ETEC diarrhea in weaned pigs when given prophylactically or therapeutically.

E. coli O157:H7 and *Salmonella* Infection

Phage therapy was also used to combat infection in pigs caused by *E. coli* O157:H7 (Morita et al. 2002; Jamalludeen et al. 2007) or *Salmonella* (Lee and Harris 2001; Switt et al. 2013). Nowadays, the pig industry should reduce its antibiotic use; therefore treatment with bacteriophages might pose an effective alternative. As we know, most strains of *E. coli* are harmless for host animals and live in a symbiotic way. However, there are reports pointing that swine have the potential to harbor EHEC that infect humans (Nakazawa et al. 1999; Callaway et al. 2004). In some cases, these bacteria can cause severe illness (diarrhea, hemorrhagic colitis, and hemolytic uremic syndrome) or even death in humans, for example, *E. coli* O157:H7 (Attar et al. 1998). Cornick and Helgerson (2004) also proved that swine do not have an innate resistance to colonization by *E. coli* O157:H7 and pigs infected with *E. coli* O157:H7 transmitted the microorganism to healthy pigs.

2.1.5 Phage Therapy in Equine

The available data shows that research on phage therapy in equine are focused on in vitro experiments. Anand et al. (2015) isolated and characterized lytic bacteriophage BPA6 against a pathogenic strain of *Aeromonas hydrophila*. These pathogens have been isolated from feces of normal horses (6.4%) but in some cases are responsible for pathological processes in equine, mainly septic arthritis, enteritis, and reproductive disorders (Igbinosa et al. 2012; Anand et al. 2015). Isolated bacteriophages displayed lytic activity against 8/14 (57.1%) of the *Aeromonas* spp. isolates. These results indicate that lytic bacteriophage BPA6 can be a potential tool against *Aeromonas hydrophila* pathogens and could be used as biocontrol agent in equine environment.

2.2 Aviculture

2.2.1 Current Challenges of Poultry Industry: Bacteria, Antibiotic Use, and Drug Resistance

Aviculture is currently the basis of the world's protein production as consumption of poultry meat has been growing for the last 50 years (Clavijo and Florez 2018, Table 1, Fig. 1). It is estimated that poultry production may reach 130 million tons of meat by 2020 (OECD). To meet the demands of growing world's population, breeders focused on such traits as fast growth, breast meat yield, and efficiency of feed conversion rates (Fadiel et al. 2005; Borda-Molina et al. 2018). Furthermore, chicken feed is heavily supplemented with amino acids, vitamins, enzymes, and probiotics in order to improve growth performance (Borda-Molina et al. 2018). Until recently, the use of growth-promoting antibiotic (GPA) was also allowed in aviculture (FDA 2000). Subtherapeutic concentrations of antibiotics increased animal production by stabilizing the gut microbiome and allowing the bird to obtain more nutrients from the diet (Dibner and Richards 2005; Lu et al. 2008; Díaz-Sánchez et al. 2015). However, this practice was shown to allow foodborne pathogens to develop antibiotic resistance (Singer and Hofacre 2006; Diarra et al. 2010; Singh et al. 2010; Schwaiger et al. 2012; Mehdi et al. 2018).

Several species of bacteria capable of causing foodborne illnesses in humans are commonly present in chicken intestine, most importantly *Campylobacter* and *Salmonella* (Atterbury et al. 2007; Oakley et al. 2014). *Campylobacter* is not considered to be pathogenic in avian hosts (Stern et al. 1995; Lee and Newell 2006). *Salmonella enterica* is generally believed to be a minor taxon in chicken gut, sporadic in distribution, and present only temporary (Liljebjelke et al. 2005; Oakley et al. 2014). This species can cause disease in chickens, depending on type of serovar and health condition of the bird (Hernandez et al. 2012; Clavijo and Florez 2018). Most human cases of salmonellosis and campylobacteriosis are caused by consumption of contaminated meat. Contamination is usually a result of a carcass coming into contact with feces of an infected animal (Wegener et al. 2003; Capparelli et al. 2010).

Furthermore, *Salmonella enterica* serotype Gallinarum and certain strains of *Escherichia coli* can cause severe infections in chickens (Dho-Moulin and Fairbrother 1999). Colibacillosis, caused by *E. coli*, is a severe respiratory and systemic infection of farmed poultry. Signs of colibacillosis are respiratory distress, reduced appetite, and poor growth. Postmortem foamy exudate and caseous exudate are observed in bird's air sac (Dho-Moulin and Fairbrother 1999; Knobl et al. 2001). *Salmonella enterica* serotype Gallinarum is a pathogen responsible for fowl typhoid (FT), a disease characterized by acute systemic infection with mortality reaching up to 80% of birds affected (Kwon et al. 2010; Filho et al. 2016). Both these diseases are responsible for heavy economic losses in the industry (Oliveira et al. 2009; Kumari et al. 2013).

Because of the development of drug resistance in bacteria (Liljebjelke et al. 2017; Nhung et al. 2017; Mehdi et al. 2018), and due to the fact that antibiotics may have a negative impact on the environment (Gonzalez Ronquillo and Angeles Hernandez 2015) and consumers health (Chan 1999; Kummerer 2009; Mehdi et al. 2018), the

EU banned the use of antibiotics as growth promoters in 2006 (EU regulation No 470/2009), and FDA enforced limitation on use of antibiotics in food animals (FDA 2005, 2012; Díaz-Sánchez et al. 2015). Therefore, there is a need to find alternative ways to prevent diseases in avian farms and contamination of food products, and alternative ways of fighting bacteria are being researched.

2.2.2 Phage Therapy in Aviculture: Experiments on Bird Models

The most common bacteria responsible for foodborne infection in humans derived from poultry are *Salmonella*, *Campylobacter*, and *Escherichia coli*. A considerable percentage of isolates are resistant to antibiotics, due to their misuse, discussed in the previous paragraph (Wernicki et al. 2017; EFSA and ECDC Report 2015). The use of bacteriophages to eliminate those pathogens seems promising as phages are present in every ecosystem, and thus they are easy to obtain, and they are more specific than antibiotics (Brussow and Kutter 2005; Loc-Carillo and Abedon 2011). Furthermore, since the use of phages in treatment of infections caused by multidrug-resistant bacteria in humans has a high success rate (Weber-Dąbrowska et al. 2000; Kittler et al. 2017; Lin et al. 2017; LaVergne et al. 2018) and phages are effectively being used in food safety (Gracia et al. 2008; Sillankorva et al. 2012; El-Shibiny et al. 2017), their application in disease prevention of poultry seems to be a logical consequence.

Salmonellosis

Salmonellosis is one of the diseases that is most commonly associated with contaminated poultry meat and eggs. *Salmonella enterica* is divided into over 2500 serovars, with different level of pathogenicity (Gal-Mor et al. 2014). In case of many *Salmonella* serotypes, birds often act as a carrier, without developing illness symptoms. There are however serovars, like *S.* Gallinarum and *S.* Pullorum, that can be a cause of serious infections in bird (Dho-Moulin and Fairbrother 1999; Lim et al. 2011; Tie et al. 2018). The most common serotypes responsible for the disease in humans are *S.* Typhimurium and *S.* Enteritidis. Other serotypes vary from one continent to another and even from country to country (Tindall et al. 2005; Feasey et al. 2012; Gal-Mor et al. 2014).

Use of phages against *Salmonella* proved to be effective on a number of occasions. 100% efficacy in eliminating *S.* Enteritidis strains from the tonsils of quails was reported by Ahmadi et al. (2016). Birds were given orally 100 ml of phage suspension (10^9–10^{10} PFU/ml) for 3 days, and the therapeutic effect was visible within first 6 h after experimental infection (Ahmadi et al. 2016). Single dose of 10^{11} phage particles administrated orally decreased the occurrence of *S.* Enteritidis in chickens by 3.5 log units (Fiorentin et al. 2005). Positive effect of phage administration as feed additive was observed in combating infections induced by *S.* Gallinarum in flocks of laying hens. The use of bacteriophages led to a drop in mortality from 30 to 5% (Lim et al. 2011). Phage YSP2 was reported by Tie et al. (2018) to have a therapeutic potential against diarrhea in chickens caused by *S.* Pullorum as the dose of 10^{10} PFU/ml reduced mortality in chickens from 50 to around 20%. However, the phage was reported to be less effective in treatment of *S.* Pullorum infection than furazolidone

(Tie et al. 2018). Some studies suggested that phages may be used in combined treatment with other preparations, such as probiotics. A mixture of three phages applied together with probiotic to combat *S.* Typhimurium infections in broilers indicated strong synergistic antibacterial effect (Torro et al. 2005). In another study, simultaneous application of three phages by aerosol spray (two doses at 6 days of age) and probiotics (single dose at 1 day of age) reduced intestinal colonization with *S.* Enteritidis (Borie et al. 2009).

However, the effectiveness of phage therapy may strongly depend on a number of factors such as the serotype of *Salmonella* causing infection, individual properties of a phage, adaptive mechanisms of the bacteria, treatment schedule, and phage dose (Capparelli et al. 2010; Bardina et al. 2012; Wernicki et al. 2017). Some studies reported only short-term effectiveness of phage therapy due to development of resistance to the bacteriophage by the bacteria (Andreatti Filho et al. 2007; Capparelli et al. 2010). On the other hand, in some cases, resistance acquisition resulted in the loss of virulence of *Salmonella* (Capparelli et al. 2010). In some cases, the treatment proved to be ineffective in reducing Salmonella colonization of birds; however bacterial isolates were determined to be phage susceptible and have not yet developed the resistance. These results suggest that there may be limiting parameters other than resistance (Hurley et al. 2008). Experiments performed by Bardina et al. (2012) focused on the impact of phage administration schedule in reducing colonization of poultry. Chickens were divided into three groups. One received a single dose of phage 8 h prior to the infection with *S.* Typhimurium, and the other received three doses (4 h prior and then at 7th and 10th day after the infection). The third group received treatment simultaneously with bacterial inoculation and at 6, 24, and 30 h after the infection. Even though concentration of *S.* Typhimurium dropped in groups 2 and 3, only in group 3 a significant decrease in mortality was observed (from 100 to 50%). In cases of groups 1 and 2, all chickens eventually died, though it occurred later than in the case of untreated chickens (Bardina et al. 2012).

Campylobacteriosis

Campylobacteriosis, caused by *Campylobacter jejuni* and *Campylobacter coli*, is currently the most common foodborne disease. These bacteria constitute a larger portion of the bacteria colonizing the gastrointestinal tract in poultry (up to 80%) (Friedman et al. 2000), and it is estimated that even up to 85% of processed meat may be contaminated with *Campylobacter* bacteria (Firlieyanti et al. 2016). One of the first studies on the efficacy of phages in treatment of *Campylobacter jejuni* colonization of poultry showed an immediate reduction of CFU counts in chicks receiving oral treatment immediately after bacterial inoculation. In case of adult birds, colonization by *C. jejuni* was inhibited, by 2 and later by 1 log unit in broiler ceca. Unfortunately, phage administration prior to bacterial inoculation did not prevent colonization. However, the study has shown that it may delay the spread of bacteria (Wagenaar et al. 2005). Similar results were observed when a suspension of phages infecting *C. jejuni* and *C. coli* was added to chicken water or feed. Administration of phages caused a 2 $\log_{10}$ CFU/g decrease in colonization, and the effect was maintained for over a week. However, preventive treatment again did

not stop colonization and only delayed it (Carvalho et al. 2010). In another study, a considerable but short-termed reduction in CFU was obtained in the intestines of birds infected with *C. jejuni* and then treated with phage cocktail consisting of two phages. Best results were obtained when bacteriophages were given to birds at final concentration of 10^7–10^9 phage particles (Loc Carillo et al. 2005). Similar results were obtained in two other studies involving infections with *C. jejuni* and *C. coli* (Atterbury et al. 2005; El-Shibiny et al. 2009). Firlieyanti et al. (2016) performed an experiment involving the use of phages on chicken liver. They observed that reduction in viable count of *C. jejuni* was modest and ranged between 0.2 and 0.7 $\log_{10}$ CFU/g (Firlieyanti et al. 2016). In regard to resistant development, it was observed by different research groups that the level of phage resistance of *Campylobacter* is rather low, reaching about 4% (Loc Carillo et al. 2005) or 13% (Carvalho et al. 2010). However, different results were presented by another research group. Fisher et al. (2013) conducted a study focusing on comparison of development of bacterial resistance to single phage and phage cocktail against *C. jejuni*. In all three trials involving broiler chicken, the level of phage-resistant *C. jejuni* reached from 43 up to 90%. The use of phage cocktail did not prevent bacteria from developing the resistance, but delayed and lowered the emergence of resistant isolates. However, they have also observed that even though phage-resistant bacteria emerged, the level of colonization was lower than in non-treated birds (Fisher et al. 2013). It was therefore speculated that development of resistance may reduce colonization capability of bacteria (Loc Carillo et al. 2005; Fisher et al. 2013).

Colibacillosis

One of the first studies involving the use of phages against colibacillosis in chicken focused on sepsis, which untreated results in 100% mortality. Intramuscular injection of phages at doses of 10^6 and 10^4 PFU/ml was shown to completely eliminate mortality of chickens with sepsis caused by *E. coli* (Barrow et al. 1998). However, since colibacillosis is a disease that develops primarily in bird's air sack (Dho-Moulin and Fairbrother 1999), phage therapy of avian pathogenic *E. coli* focuses mostly on using aerosol and direct application to bird's air sac. Phage mixture applied to air sac of 7-day-old birds was able to reduce mortality by 50%. In chicks (1–3 days of age), the use of aerosol decreased mortality from 20 to 3%. However, there was no significant difference in case of birds challenged at 8, 10, or 14 days old (Huff et al. 2002a). In another study performed by the same group, chicks were infected with 10^4 CFU/ml of *E. coli* and treated with aerosol containing phages at titers of 10^4 and 10^2 PFU/ml. Use of phages reduced mortality to 35% (10^2 PFU/ml dose) and 0% (10^4 PFU/ml dose). It was also shown that this kind of treatment can be successful when applied in ovo, and its results are comparable to standard treatment using enrofloxacin (Huff et al. 2004, 2009). It was also demonstrated that combined use of enrofloxacin and phage cocktail has a synergistic protective effect in chickens (Huff et al. 2004). Huff et al. (2002b) also suggested that phages distributed in form of aerosol can be used as a preventive measure before possible infection might happen, i.e., before transport. In order to achieve the highest effectiveness, phages should be administrated to birds 1–3 days before being exposed to putative risk factor (Huff

et al. 2002b). Research performed by Oliveira et al. (2009, 2010) addressed the efficacy of phage treatment depending on administration route and phage type and titer used. It was observed that sprayed phages were able to reach the respiratory tract within 3 h after administration. In case of oral administration, phages were able to reach lungs; however, some of the phages were also found in other internal organs, i.e., liver and duodenum. Moreover, intramuscular injection resulted in phage presence in all organs collected (Oliveira et al. 2009). In another experiment, chickens were given a suspension (10^9 PFU/ml) of one of three phages, either by oral application or by spraying directly into the beak. Birds were infected with pathogenic *E. coli* immediately after phage distribution. One phage in particular, phi F78E, administered both orally and by spray, resulted on average in a 25% decrease in mortality (Oliveira et al. 2010). Therefore, spray and oral administration are recommended in order to control respiratory infections caused by *E. coli* (Oliveira et al. 2009, 2010). Skaradzińska et al. (2017) have also performed in vitro tests on *E. coli* carrying plasmid encoding resistance to β-lactam antibiotics isolated from turkey farms. This research group found that phages isolated from litter samples were effective against antibiotic-resistant strains of *E. coli* isolated from turkey farms in Poland. However, experiments analyzing effectivity of those phages in vivo still need to be performed (Skaradzińska et al. 2017). It was also shown that phages can be effectively used as a means of protection against colibacillosis by spraying the chicken pens. 200 ml of phage suspension at a titer of 8×10^8 on the litter and surface of the pen reduced mortality of 3-week-old broilers (El-Gohary et al. 2014). It is therefore suggested that use of phage suspension to spray chicken pens may be an effective way to prevent *E. coli*-associated diseases in chicken (Oliveira et al. 2010; El-Gohary et al. 2014; Wernicki et al. 2017).

Other Diseases

Phage therapy was also used to combat Gram-positive bacteria found in poultry: *Clostridium perfringens* and *Listeria monocytogenes* (Wernicki et al. 2017). While in case of *L. monocytogenes* research mainly focus on the use of phage cocktails on processed meat (Housby and Mann 2009; Bigot et al. 2011), there have been a few studies conducted on chicken model regarding phage therapy against *C. perfringens*. Miller et al. (2010) showed that phage treatment of chicken infected with *C. perfringens* was even more effective in reducing mortality than commonly used vaccine against this bacterium. In another study, a combined treatment of a phage cocktail and endolysins was applied. Combination of phages and murein hydrolase enhanced the performance of a phage, and lytic effect was observed against all ($n = 51$) strains tested (Zimmer et al. 2002a, b). However, there are still very few studies regarding phage therapy against *C. perfringens*, and more data is needed to fully evaluate its performance (Wernicki et al. 2017).

2.2.3 Phage Therapy in Aviculture: Applications to Market

Due to EU policy regarding the use of bacteriophages in disease prevention, there is currently no phage-based product to be used in aviculture in counties that are EU members (Debarbieux et al. 2016). However, Proteon Pharmaceuticals, a Poland-

based company, released phage cocktail that is commercially available in Russia and Ukraine. The product, BAFASAL®, can be used as feed or water additive and is a mixture of phages infecting some of the most common *Salmonella enterica* serovars, including Enteritidis, Typhi, Paratyphi, Typhimurium, Brandenburg, and Hadar (Wójcik et al. 2015). Tests performed on a total number of 220 broilers showed a significant decrease in the number of *Salmonella* Enteritidis in gastrointestinal track of chickens (Proteon Pharmaceuticals report). BAFASAL® was also recently registered in the USA and is currently under the review by EU commissions.

2.2.4 Prospects and Challenges of Phage Therapy in Aviculture

Data presented by many research groups all around the world show that phage therapy may be a potential means for prevention against pathogenic colonization of birds (Wernicki et al. 2017). Phages were found to be effective in reducing mortality in bird cases of colibacillosis (Barrow et al. 1998; Huff et al. 2002a, b; Oliveira et al. 2009, 2010). These viruses lower the rate of colonization of bird's gastrointestinal tract with *Campylobacter* and *Salmonella* (Fiorentin et al. 2005; Loc Carillo et al. 2005; Atterbury et al. 2005; El-Shibiny et al. 2009; Ahmadi et al. 2016) and prevent the birds from developing systemic illnesses caused by some *Salmonella* serotypes (Lim et al. 2011; Tie et al. 2018). However, use of phage therapy as a widespread means for prevention of diseases is still under debate. One of the problems is the fact that even though phages reduced bacterial count in bird's gastrointestinal tract, in some cases, re-emergence of bacteria was observed after a few days (Wagenaar et al. 2005; Fisher et al. 2013). The results also seemed to depend strongly on the type of phage, dose, and time of administration (Oliveira et al. 2009; Capparelli et al. 2010; Bardina et al. 2012). Therefore, more research is needed in order to determine a procedure that will bring the best possible results. There is also more research needed on phage resistance development and phage-bacteria coevolution. Understanding those mechanisms may help in phage applications in the future.

Phage development, properties, and genetic material need to be analyzed in depth before viruses can be used in phage therapy. This procedure is time-consuming, and not all isolated phages fulfil necessary requirements (Zhang et al. 2013; Lee et al. 2016; Skaradzińska et al. 2017). Furthermore, phages infecting some of the taxa are harder to isolate than the others. For example, phages infecting *Campylobacter* spp. are often difficult to isolate and to propagate in laboratory environment, and large number of samples need to be analyzed in order to find a suitable phage (Janez and Loc Carillo 2013; Firlieyanti et al. 2016; Sorensen et al. 2017; Gencay et al. 2017). There are also reports showing that the choice of the primary isolation strain may bias the selection of bacteriophages (Sorensen et al. 2015). Therefore, phage cocktail needs to undergo many trials in order to test its efficacy and safety before it can become an actual product.

Furthermore, regulations of the European Union do not fit bacteriophage therapy and use of phages adequately. Therefore, phages cannot be used as a common alternative to antibiotics or other antimicrobial compounds. Until the regulations will not be

adapted, commercially available phage products will most likely not be available in countries that are EU members (Debarbieux et al. 2016; Fauconnier 2017).

2.3 Aquaculture

The Food and Agriculture Organization (FAO 2016) showed that aquaculture is one of the most rapidly growing sectors for animal food production, supporting approximately 50% of the global human fish consumption. Aquaculture continues to grow more rapidly than any other animal food-producing sectors. The growing demand for fish and shellfish as well as the more stringent rules on wild catches has led to increased production in the aquaculture sector (Thompson et al. 2004). Aquaculture is becoming one of the fastest growing productive sectors, providing nearly one-third of the world's seafood supplies (Kramer and Singleton 1992). Unhygienic food practice causes foodborne disease and also can damage, infect, or even kill marine products. It makes huge financial losses (Richards 2014).

Currently, the use of disinfectants and antibiotic on a large scale is very popular to prevent bacterial diseases in marine organisms. This has led to environmental pollution by the remains of antibiotics remaining in seawater and the presence of antibiotic-resistant bacteria (Kalatzis et al. 2018). In fact, in the marine environment, the majority (90%) of bacterial strains are resistant to more than one antibiotic, and 20% are resistant to at least five antibiotics (Lagana et al. 2011). Therefore, alternative strategies to the use of antibiotics should be developed to combat problems associated with treatment and prevention of diseases in aquaculture (Weber-Dąbrowska et al. 2016). Phage therapy may be a promising alternative for this, but its use in aquaculture requires a detailed observation of the seasonal dynamics of the total bacterial communities, the microbiological water quality, and the presence of pathogenic bacteria in the water system (Pereira et al. 2011). All-year observations have shown the higher complexity of the whole bacterial structure and the emergence of new populations of the main pathogenic bacteria of fish during the warm season, especially in the spring (Pereira et al. 2011).

2.3.1 Pathogenic Bacteria in Aquaculture

There are two groups of bacteria which contaminate aquaculture products: naturally occurring in the aquatic environment (e.g., *Clostridium botulinum*, *Listeria monocytogenes*, *Aeromonas hydrophila*, *Vibrio parahaemolyticus*, *Vibrio vulnificus*, and *Vibrio cholerae*) and introduced from outside by animal waste, sewage, or industrial sources (e.g., *Enterobacteriaceae* such as *Escherichia coli*, *Shigella*, and *Salmonella*) (Fukuda et al. 1996; Nakai et al. 1999; Nakai and Park 2002). The biggest threats to fish are vibriosis and photobacteriosis—fish disease caused by local bacterial species from the genera *Photobacterium*, *P. damselae*, and *Vibrio*, *V. alginolyticus*, *V. vulnificus*, *V. salmonicida*, and *V. parahaemolyticus* (Moriarty 1998; Defoirdt et al. 2007). These diseases can cause significant mortality in fish, reaching values of up to 100% in infected facilities. Significant numbers of those bacteria remain on the skin of marine organisms and may harm consumer's health also (Kalatzis et al. 2018).

2.3.2 The Use of Bacteriophages in the Treatment and Prevention of Infections in Aquaculture

Phage therapy may be a promising strategy for controlling diseases in aquaculture (Subharthi 2015). The available literature indicates that phages have been successfully used to control pathogenic bacteria in water environment (Matsuzaki et al. 2005; Kalatzis et al. 2018; Wu et al. 1981; Pal et al. 2016; Skurnik and Strauch 2006). Bacteriophages were first used to treat infections of *Aeromonas hydrophila* in eel's redfin. After 3-h infection of phage AH1, the *A. hydrophila* had completely lost its infectivity and mortality (Wu et al. 1981). Next, phage therapy was used in yellowtail in the aquatic culture in Japan against *Lactococcus garvieae* in 1999 (Nakai et al. 1999). Since then, many scientists want to find more and more phages against pathogenic bacteria that infect marine organisms.

Phage Therapy in Fish

The use of phages to prevent fish infection is well documented (Silva et al. 2014b; Pal et al. 2016; Nakai et al. 1999; Stevenson and Airdrie 1984; Wu et al. 1981; Park and Nakai 2003; Nakai and Park 2002). Several groups demonstrated therapeutic efficacy of phage therapy against infectious diseases caused by *Pseudomonas plecoglossicida*, *Enterococcus seriolicida*, *Aeromonas salmonicida*, *Pseudomonas aeruginosa*, *Photobacterium damselae*, and *Lactococcus garvieae*. These infections affect marine fish, such as seabream (*Sparus aurata*), Atlantic salmon (*Salmo salar*), and rainbow trout (*Oncorhynchus mykiss*) (Higuera et al. 2013; Nakai et al. 1999; Park et al. 2000; Park and Nakai 2003; Almeida et al. 2009; Gudding and Van Muiswinkel 2013).

Nakai and Park described the successful use of phages against *Enterococcus seriolicida* infection of yellowtail and *Pseudomonas plecoglossicida* infection of ayu (Nakai and Park 2002; Park and Nakai 2003). Both bacterial species are typical opportunistic pathogens because they are ubiquitous in fish and their culture environments (Nakai and Park 2002). In recent years, various groups have paid attention to the infection caused by *Flavobacterium*. Madsen et al. (2013) have shown that phage FpV-9 protected fish against *Flavobacterium psychrophilum*, the Gram-negative fish pathogen responsible for rainbow trout fry syndrome (RTFS) in salmonid hatcheries worldwide. Another group found FCP1 phage isolated from fish farm, active against *Flavobacterium columnare* bacteria, which causes cottonmouth disease in fish (Prasad et al. 2011).

Phage Therapy in Seafood

Seafood is also exposed to contamination with bacteria. Most of oysters or shrimp produced in Australia are distributed live and are frequently eaten unclean or raw or lightly cooked (Mohamed et al. 2003). Hence, human pathogens may not be removed and can be eaten with food, causing various human diseases. Thus, pathogenic bacteria such as *Escherichia coli*, *Campylobacter*, *Staphylococcus*, and *Salmonella* species can be easily transferred (Hatha et al. 2005; Pal et al. 2016).

These bacteria may cause severe infections, leading to a relatively high level of morbidity and mortality. One of them, caused by enterotoxigenic *E. coli*, was reported in sushi restaurants in Nevada (USA) in 2004, where 130 patients

developed severe symptoms like diarrhea or vomiting (Jain et al. 2008). The consumption of butterfly shrimp and oysters was identified as the most likely vehicle of infection. Le et al. (2017) used the bacteriophage cocktail in controlling *Escherichia coli* strains and *Salmonella enterica* contaminants of the edible oysters. The used phages (five different *E. coli*-specific phages from *Siphoviridae* family and a *Salmonella*-specific phage from *Tectiviridae* family) resulted in significant decrease of the number of these bacteria on edible oysters (Le et al. 2017). Therefore, phage treatment might be an effective tool to ensure safety of aquaculture produce.

Phage Therapy in Coral Reefs

One of the most diverse and important water ecosystems on earth is coral reefs (Bryant et al. 1998). However, infectious diseases contribute to a decrease in their quantity (Kerri et al. 2004; Doss et al. 2017). Thus, phage therapy was also used against pathogens in corals, such as *Thalassomonas loyana* which cause bleaching and white plague-like disease. Phage BA3 inhibited this infection and transmission of this disease from one coral to the others (Efrony et al. 2009; Barash et al. 2005; Thompson et al. 2006). The growth of bacteria *Vibrio coralliilyticus*, causing the tissue lysis of the coral, was also inhibited with the use of specific bacteriophages (Ben-Haim et al. 2003).

2.3.3 Vibrios in Aquaculture

One of the main threats to marine organisms is vibriosis, caused by bacteria of the *Vibrio* genus (Goulden et al. 2012; Schiewe et al. 1981; Toranzo et al. 2005). The main factors causing epidemics are *V. cholerae*, *V. parahaemolyticus*, *V. vulnificus*, *V. harveyi*, *V. parahaemolyticus*, *V. alginolyticus*, *V. vulnificus*, and *V. splendidus* (Thompson et al. 2005; Seed et al. 2014; Kalatzis et al. 2018; Plaza et al. 2018). Diseases caused by vibriosis, including early mortality syndrome (EMS) or acute hepatopancreatic necrosis disease (AHPND), contribute to losses in the aquaculture industry (Kalatzis et al. 2018). Many previous reports indicated that phage therapy is an effective treatment against vibriosis disease.

Bacteria of the genus *Vibrio* usually enter larval-rearing water through live feeds, such as *Artemia* and rotifers (Kalatzis et al. 2016). Live foods are able to swim in water column and are available to fish and shellfish larvae thereby Rasool et al. 2014). Live feed, like *Artemia*, can also accumulate bacteria from the water column and can transfer the pathogenic and resistant strain into the hatchery (Maleknejad et al. 2014). Therefore, phage therapy is also helpful in this case, to control the number of *Vibrio* bacteria in the live feeds prior to their introduction in the hatchery system. One of the main pathogenic species in larval rearing is a ubiquitous bacterium *V. alginolyticus*. Kalatzis et al. (2016) isolated two novel broad host range lytic bacteriophages φSt2 and φGrn1 from this bacterium. These viruses are able to infect all host strains and also *V. harveyi* and *V. parahaemolyticus* species (Kalatzis et al. 2016; Andrews and Harris 2000). Similar research has been carried out during the production of fish larvae of zebrafish—*Danio rerio*—experimentally exposed to *V. anguillarum* (Cantas et al. 2012; Silva et al. 2014b; Higuera et al. 2013).

It was found that phages prevented the infection by vibrios without affecting the beneficial bacterial community.

Additionally, some bacteria, such as luminous *Vibrio harveyi*, cause serious mortalities. Four bacteriophages were isolated, three from oyster tissue and one from shrimp hatchery water. The bacteriophage treatment resulted in over 85% survival of *Penaeus monodon* larvae infected with *V. harveyi*, suggesting that bacteriophage therapy would be an effective alternative to antibiotics in shrimp hatcheries (Karunasagar et al. 2007; Vinod et al. 2006).

Wang et al. (2017a, b) demonstrated that two *Siphoviridae* phages can eliminate *V. harveyi* strains infecting abalone (*Haliotis laevigata*). The effect of phage therapy on vibriosis in Atlantic salmon (*Salmo salar*) was also tested. The bacteriophage CHOED was found, which provided 100% protection of the fish against *V. anguillarum*, when MOI 1 and MOI 10 were use. What is important, untreated fish suffered over 90% mortality (Higuera et al. 2013).

Infections by *Vibrio* have been observed also in the sea cucumber (*Apostichopus japonicus*)—marine animals which are used for food. *A. japonicus* was cultivated on a commercial scale in northern China, where production reached 5865 tons in 2002. However, the rapid expansion of the aquaculture by *Vibrio* species contributes to economic loss. It was demonstrated that phage isolated from the raw sewage obtained from the drain pipes from the local hatchery of sea cucumber controls infections caused by *V. cyclitrophicus*, *Vibrio alginolyticus*, and *Vibrio splendidus* (Li et al. 2016a–c; Zhang et al. 2015a).

The team from Malaysia found a novel vibrio phage (VpKK5), from *Siphoviridae* family, that was lysing the *V. parahaemolyticus* strain, pathogenic to shrimp and tropical cultured marine finfish. The KVP40 phage is also worth attention (Lai et al. 2016). Matsuzaki et al. (1992) showed that this myovirus has a broad host range, which may mean that a number of different *Vibrio* species have a receptor for the phage in common. This phage is able to infect several strains of different *Vibrio*: *V. alginolyticus*, *V. cholerae*, *V. parahaemolyticus*, *V. anguillarum*, *V. splendidus*, *V. mimicus*, *V. natriegens*, and *V. fluvialis*.

However, most of the presented reports focused on the isolation and characterization of phages capable of reducing the pathogenic bacteria in aquaculture only in vitro. So, it is necessary to carry out more in vivo tests to fully prove the advantages of using phage therapy. Thanks that it will be possible to produce and approve phage-based preparations against infections in aquaculture. At present, such therapeutics are not available.

2.3.4 Phages Delivery Method

Phages have different abilities to maintain their lytic potential against pathogens and to reach target organs of adequate density. Hence, the phage delivery methods are of vital importance for a successful therapy. According to the available literature, it is known that phages can be administered in three different ways: parenteral delivery, oral administration, and immersion in a bath containing phages.

Intramuscular injection of phage (parenteral delivery) has proven to be one of the most successful delivery methods in animal studies, because the phages can

immediately reach the systemic circulation (Ryan et al. 2011). It was reported that bacteriophages could be detected in the fish tissues for several days after administration (Nakai and Park 2002; Madsen et al. 2013). For example, the results obtained by Prasad et al. (2011) suggest that intramuscularly route of phage introduction resulted in reduction of clinical symptoms and a better lytic impact on bacterium, relative to other delivery methods. What is important, to spread phages to all the internal organs via the circulatory system, a high phage concentration is necessary. However, this method is labor intensive, including work with small animals, and may be rather stressful for water organisms (Christiansen et al. 2014; Kalatzis et al. 2018).

Orally administered phage through phage-impregnated food allows continuous supply with a large amount of marine organisms (Oliveira et al. 2012). The main problem with this method is phage stability in the highly acidic and proteolytically active environment of the stomach. Research performed by Christiansen et al. (2014) demonstrated that orally administered phages can penetrate the intestinal wall and be absorbed into the circulatory system. Phages were detected in the kidney, spleen, and brain after the application. This method resulted in constant, high abundance of phages in the fish organs for several weeks (Christiansen et al. 2014). Additionally, studies with the use of goldfish have shown that phages are capable of penetrating the intestinal wall (Kawato and Nakai 2012). Phage-coated feed has been successfully used also for treating *Pseudomonas plecoglossicida* infections in ayu and *F. columnare* infections in catfish (Park and Nakai 2003; Nakai and Park 2002; Prasad et al. 2011). Furthermore, Christiansen et al. (2014) reported that continuous delivery of the feed pellets coated with phage FpV-9 is a successful method for prevention of rainbow trout fry syndrome caused by *F. psychrophilum.*

The conditions in gastrointestinal tract are unfavorable for phages, which can affect the phage viability (Christiansen et al. 2014). During the phage delivery by oral route, the problem is phage stability in the highly acidic and proteolytically active environment of the stomach, because each phage can have different sensitivity to pH (Kim et al. 2010; Ryan et al. 2011; Bucking and Wood 2009).

It was found that in aquaculture, oral administration is the most cost-effective delivery method for immunization due to low cost and less stress to fish (Yasumoto et al. 2006; Nakai and Park 2002; Park et al. 2000; Martínez-Díaz and Hipólito-Morales 2013).

In fish larviculture, supplementation of phages by oral administration or parenteral delivery is difficult. Therefore, viruses must be directly released into the culture water (Silva et al. 2014b). The survival of phages in these conditions must be high. The fish larvae are immersed in a bath containing a high titer of phage. Thanks that phages can reach the specific site of infection. Additionally, marine fish species drink water to maintain their internal ionic balance, and therefore, phages present in the water have the opportunity to encounter pathogenic bacteria for which the infection route is through the fish intestinal mucosa (Christiansen et al. 2014). This can be exemplified by research conducted by Silva et al. (2014b) with the use the phage VP-2 against *V. anguillarum* in fish larviculture. This phage is able to survive for long time (at least 5 months) in marine water. Additionally, due to releasing this virus directly into the water, phage can control the bacterial colonization not only

inside fish but also on fish larvae skin (Silva et al. 2014b; Weber et al. 2010). Therefore, this method allows to simultaneously reduce pathogens within the animal and in its immediate environment (Richards 2014).

The choice of the appropriate and the most successful method of phage administration in aquaculture depends on the conditions prevailing in aquaculture and should be adapted to each organism and pathogen separately. New dimensions in phage application in aquaculture may be phage cocktails. For example, Chan et al. (2013) and Defoirdt et al. (2007) have observed that a mixture of different phages, i.e., phage cocktails, is more effective for treatment of bacterial infections. Thus, the spectrum of virus activity is expanded and overcomes the resistance to adherence of phage by the pathogenic host bacteria (Le et al. 2017). Hence, mixtures or cocktails of phages may be useful to prevent the development of phage-resistant pathogens in aquaculture.

2.3.5 Concerns About Phage in Aquaculture

The increasing temperature in the oceans, and the fatal effects of vibriosis and other pathogenic bacteria on aquaculture, causes that using the phages to control this problem is very important. Phage therapy has many advantages. The most important are fast phage isolation procedures and reasonably inexpensive methods which are both environment- and consumer-friendly. However, phages have also the potential risk factors, like dispersal of unwanted genes or effects on fish microbiota (Kalatzis et al. 2018). A serious threat to marine organisms can also be endotoxins. They might be potentially toxic for fish or shellfish (Opal 2010; Boratyński et al. 2004).

Another problem with using the phages in aquaculture might be the immune response. In water organisms, such as fish, the immune system may contribute to phage decay (Pirisi 2000). In available literature, there is little information about production of antibodies after phage delivery in aquaculture (Oliveira et al. 2012). This problem was addressed in only a few studies. When phages were used against infection in yellowtail (Nakai et al. 1999) and in ayu (Park and Nakai 2003), no bacteriophage-neutralizing antibodies were detected.

On the other hand, fish larvae do not have the ability to develop specific immunity (Vadstein 1997); thus, the immune system cannot remove the phage particles from circulatory system (Duckworth and Gulig 2002). Similarly, corals have no adaptive immune system; therefore, the use of phages against corals pathogens is practical (Kerri et al. 2004; Efrony et al. 2009; Nair et al. 2005).

For other organisms living in water, like sea cucumbers and other echinoderms, phagocytes and bulbous cells are the major line of defense against pathogens. Nitric oxide synthase and acid phosphatase are the main defense enzymes of these cells. They change when the organism is infected with pathogens. Li et al. (2016b, c) demonstrated that feeding phages of infected sea cucumbers provoked partial immune response, but there is no effect on the normal growth of sea cucumbers (Dolmatova et al. 2004; Li et al. 2016b, c).

In summary, all these reports demonstrated that it is necessary to select the appropriate phage to perform effective phage therapy. Latent period of phages, burst size, lytic potential, phage time of survival in the water, host range of the

phage, and efficiency of bacterial inactivation are important when phages are selected. In aquaculture, the greatest success of therapy can be achieved by using phages which withstand various environmental stresses.

2.3.6 Summary of Phage Therapy in Aquaculture

Increase of aquaculture production causes the emergence of more and more cases of bacterial infections. This causes significant economic losses for the industry. Microbial diseases have caused mass mortality of fish and other marine organisms (Kalatzis et al. 2018). The increasing use of antibiotics has led to severe negative side effects, like the selection of resistant bacterial strains. Nowadays, several environment-friendly prophylactic methods must be developed to control diseases and to maintain healthy microbial environment in aquaculture systems. The alternative approach may be using lytic phages for the treatment or prophylaxis of bacterial infectious diseases.

The available literature reported that bacteriophages have the therapeutic potential in the control of bacterial disease for fish, finfish (Park et al., 2000; Nakai and Park 2002; Park and Nakai 2003), and also seafood, like prawns (Vinod et al. 2006; Karunasagar et al. 2007), oysters, or shrimp (Le et al. 2017). Viruses also have been used against bacterial infections of coral reefs with promising results (Efrony et al. 2009).

It has been documented that in many tested cases, phage therapy is cost-effective, eco-friendly, and safe for aquacultured species and for animals. It provides the same or better protection of infected marine organism than antibiotics. This is exemplified by phage trials in a commercial shrimp hatchery using two lytic *Vibrio harveyi*-specific broad host range bacteriophages. Phage application caused about 87% shrimp survival, while in antibiotic-treated (oxytetracycline and kanamycin) shrimp, the survival was 67% (Karunasagar et al. 2007). Another group presented the results with the use of lytic bacteriophages against pathogenic *Vibrio splendidus* strains in *Apostichopus japonicus*. They reported that 18% animals survived the infection when using the control diet and 82% survived after antibiotic-supplemented or phage cocktail-supplemented diet (Li et al. 2016b, c).

Therefore, phage therapy seems to be a promising alternative to the use of antibiotics in aquaculture. This approach is important in production processes to obtain products with reduced bacterial loads or to limit current pathogenic bacteria in water. Additionally, prophylactic using of phages can improve microbiological water quality. This is a successful method to control pathogenic bacteria in aquaculture.

2.4 Brief View of Methods for Phage Preparation

2.4.1 Phage Isolation

The prevalence of bacteriophages in environment is a great advantage of using phages against bacteria over other antimicrobial agents. Every environmental sample containing pathogens in which we are interested in presumably contains a phage

(or phages) that can infect and lyse bacteria. Due to high concentration of microorganisms, the most common source of bacteriophages is urban sewage (Jurczak-Kurek et al. 2016; Li et al. 2016a; Switt et al. 2013; Abatángelo et al. 2017), but phages can also be easily isolated from rivers, from wastewater of clinics and hospitals, or directly from organisms (Bachrach et al. 2003; Merabishvili et al. 2012; Bhetwal et al. 2017).

Phage isolation is usually simple, quick, and inexpensive in comparison to other antimicrobials (Skurnik et al. 2007; Loc-Carillo and Abedon 2011). There are a lot of methods to acquire bacterial viruses, but all of them are based on the similar pattern (Gill and Hyman 2010). The most direct way is sterilization of environmental sample to remove cellular microorganisms, by using centrifugation or filtering through the membrane filter. In the most cases, sterilized sample is added directly to host strain (s) and plated by double agar overlay plaque assay to estimate the appearance of plaques (Kropinski et al. 2009). Spot assay also can be used, but it may overestimate both the overall virulence and the host range (Mirzaei and Nilsson 2015). In the next step, single plaque of isolated phage should be transferred into liquid medium (Mattila et al. 2015). To improve the visibility of phage plaques, the use of sublethal doses of antibiotics is suggested especially in the case of environmental samples (Los et al. 2008; Santos et al. 2009; Kaur et al. 2012). Before plating, samples can be concentrated by precipitation with polyethylene glycol (PEG), super-speed centrifugation, tangential flow filtration (TFF), or even organic flocculation with skimmed milk (SMF), though each of these methods may influence the carriage or survival of the phage (Calgua et al. 2008; Gill and Hyman 2010; Castro-Mejía et al. 2015; Hjelmsø et al. 2017). Samples may also be enriched by culturing in the presence of one or more of the desired bacterial hosts. It allows initially small population of the phages to propagate until they reach a concentration which is easily detected by standard methods. Enrichment can be carried out by adding a sterilized liquid to a rapidly growing host culture and incubating for the time depending on the growth rate of the host. The raw sample may be added to the host culture, or the host culture may be diluted into a volume of environmental sample in such a way that host is numerically dominant in the culture (Gill and Hyman 2010). Many phages require ions such as Ca^{2+} or Mg^{2+} for attachment or intracellular growth; thus, it is important to include 1–2 mM Ca^{2+} in all the media (Van Twest and Kropinski 2009). To provide that phage isolated for therapeutic usage is able to lyse the pathogenic strain of interest, isolation should be conducted with using the same bacterial strain.

2.4.2 Phage Characterization

All isolated phages must be characterized to confirm the potential for their use in phage therapy. The first step is examining the ability to lyse other bacterial strains which were not used in the isolation process. The desired range of hosts depends on the purpose of use; like in intestinal infections, a usage of narrow host range phages is recommended to protect commensal bacteria. Describing a host range may also test if this phage can be used to treat infections with other pathogenic strains or to find the bacterial strain in which phage develops more efficiently making it easier to find the most effective procedure.

There are also some developmental features which have to be tested: adsorption rate, latent period, burst size, and morphology of plaques. Determination of phage adsorption kinetics begins with mixing phage with bacteria culture in appropriate medium and then checking free phage loss, infected-bacteria gain, or uninfected-bacteria loss over time (Hyman and Abedon 2009). The latent period is the time interval between phage adsorption and releasing the phage progeny from lysed bacteria. Measurement of phage latent period duration may be conducted by detecting the released virions or survived bacteria. It is also important to determine a burst size which represents the number of phage progeny. Both latent period and burst size can be examined in one-step growth experiment which was described in detail by Hyman and Abedon (2009). In all these experiments, it is important to use multiplicity of infection (MOI) less than 1 to prevent multiple adsorption, lysis from without, or bacteria adsorption capacity limits (Delbrück 1940; Hyman and Abedon 2009; Abedon 2011). Based on plaque morphology, we can point out phages with lytic activity. In phage therapy, temperate phages should be avoided, due to possibility of containing genes which alter the phenotype, encoding toxins or virulence factors, and ability of such phages to conduct general transduction (Scott et al. 2008; Chen and Novick 2009; Lang et al. 2012; Goh et al. 2013; Fortier and Sekulovic 2013; Navarro-Garcia 2014). Temperate phages form turbid plaques in contrast to lytic phages which form clear plaques without halo (Abedon and Yin 2009). It should be concerned that plaque morphology depends on many factors like growth phase of the bacterial host or diffusion of virions in agar plate; hence, the "lifestyle" of the phage should be also validated through genome analysis (Gill and Hyman 2010).

Current technology of DNA sequencing and the low cost of this process made phage genomic analysis easier and more accessible. Genome sequencing and characterization of each isolated phage can show the presence of virulence, antibiotic resistance, or lysogenic genes which helps to exclude phages non-usable for therapy. Nowadays, there are a lot of computational tools to predict function of viral genes or for phage identification or classification, e.g., Unipro UGENE, GLIMMER, GeneMark, or RAST (Fancello et al. 2012; Lobanova et al. 2017; Aziz et al. 2018; McNair et al. 2018; Tithi et al. 2018).

2.4.3 Phage Purification

Bacteriophages are isolated using bacteria culture, making them contaminated with unwanted culture compounds, e.g., toxins and other immunomodulators. The most basic method for purifying phage lysate is low-speed centrifugation and then filtration through membrane filter (see Sect. 2.4.1), but these preparations can induce few side effects when administrated in phage therapy (Sulakvelidze and Kutter 2005). Most protocols of purification are focused on segregation from the lipopolysaccharide (LPS), a component of Gram-negative bacterial cell membranes which is known to be an endotoxin (Cavaillon 2018). The most typical phage purification method for small-scale preparation is high-speed centrifugation in a cesium chloride gradient (Boulanger 2009; Nasukawa et al. 2017). However, this method requires long time and expensive and specialized equipment, and it is limited

by the size of probe (Gill and Hyman 2010). Moreover, some phages can be instable in the high osmotic environment (Carlson 2005). Endotoxins can also be removed by extraction with organic solvents based on the fact that phages retained in the aqueous phase, while endotoxin accumulates in the organic solvent (Szermer-Olearnik and Boratyński 2015). Another alternative method is using anion-exchange chromatography using large pore size monolithic anion exchangers and chromatography system. Sponge-like structure of columns provides a large surface area for binding and thus improving accessibility of viruses (Oksanen et al. 2012). Advances of using this method are high resolving power, high capacity, simplicity, and controllability, making this technique suitable for processing large volumes. The first protocol for this method with cellulose as an adsorbent (ECTEOLA columns) was proposed in 1957 by Creaser and Taussig (1957). Recently most of procedures are conducted with commercially available monoliths, e.g., Convective Interaction Media® monoliths or SepFast™ Supor Q with high efficiency (Kramberger et al. 2010; Monjezi et al. 2010; Adriaenssens et al. 2012; Liu et al. 2012). Another method without mechanical purification is enzymatic inactivation of the endotoxin using alkaline phosphatase (Bentala et al. 2002). However, the treatment of the phage preparations with alkaline phosphatase may have low endotoxin removal efficiency and a negative impact on the number of infectious phage (Van Belleghem et al. 2017).

2.4.4 Phage Stabilization and Formation

Phages may be unstable in aqueous solutions due to the fact that their building blocks are proteins (Chi et al., 2003), and storage method should be adapted to the phage biology and properties. The most frequently used and efficient long-term storage way of preparations is cooling (4 °C) and freezing (–20 °C, –80 °C) (Fortier and Moineau 2009). Methods with the use of lower temperatures may require addition of cryoprotectors that increase phage stability in water solutions of various compounds, like glycerol, which stiffen the structure of proteins and inhibit their aggregation. It has been used many times to preserve liquid preparations with high survival of phage (Nyiendo et al. 1974; Mendez et al. 2002), but individual cases show that this method may change their activity and titer (Clark 1962).

The preservative compounds are also used in another storage method—lyophilization (Clark and Geary 1973; Puapermpoonsiri et al. 2010). Freeze-drying is a low-temperature dehydration process based on freezing the product, lowering pressure, and ice sublimation. Lyophilization is characterized by high effectiveness for the long-term preservation of bacterial cells, stability of lyophilized preparations at room temperature, and easy transportation of phages prepared this way (Fortier and Moineau 2009). The disadvantage of this method may be the reduction in phage titer as a consequence of the freeze-drying procedure itself (Clark 1962; Ackermann et al. 2004; Dini and de Urraza 2013; Merabishvili et al. 2013). Important factors decreasing a number of survival phages are osmotic stress and ability of phage aggregation (Puapermpoonsiri et al. 2010; Louesdon et al. 2014). Despite that, phage titers of freeze-dried preparations can be stable in long-term storage, even for 2 years when stored refrigerated (Clark 1962). Merabishvili et al. (2013) tested the influence of six preservative compounds on stability of *Staphylococcus aureus* phage ISP after

freeze-drying pointing on sucrose and trehalose to be the most effective protectant in this case and that the effectiveness of stabilization depends on protectant concentration (Merabishvili et al. 2013). Some papers pointed on addition of specific particles to the phage solution, including sodium glutamate, gelatine, peptone, casein, or skimmed milk. This may increase viability of phage after lyophilization (Steele et al. 1969; Engel et al. 1974; Puapermpoonsiri et al. 2010).

Additional procedure is spray drying in which liquid preparation is atomized and converted into mist and then contacted with a hot dry gas inside a drying chamber. In this process, solvent is quickly evaporating causing formation of insoluble compounds which are phage and excipients in the form of powder. The most commonly used protectant in this procedure is trehalose, but also usage of lactose, leucine, glucose, sucrose, or mannitol was reported (Matinkhoo et al. 2011; Vandenheuvel et al. 2013; Leung et al. 2016). This method has also been shown to result in loss of phage titer due to sensitivity to thermal and shear stress (Leung et al. 2016).

Phages can be also stabilized by encapsulation in protective particles, by coating with polymers or lipids, or incorporated into the droplets (Malik et al. 2017). Most of phage encapsulation methods consist of the process of emulsification, followed by solvent removal. Emulsion can be water-in-oil (Surh et al. 2007; Kim et al. 2015), oil-in-water (Esteban et al. 2014), or water-in-oil-in-water (Surh et al. 2007; Wang and Nitin 2014; Rios et al. 2018). Droplets that contain phages can be also produced by extrusion, mostly followed with gelation process, ionotropic gelation, heating, or covalent cross-linking (Dini et al. 2012; Ma et al. 2012; Gul and Dervisoglu 2017). There are many polymers which have been used in phage encapsulation process. The most frequently used is alginate (Colom et al. 2017; Ahmadi et al. 2018; Cortés et al. 2018) due to low toxicity and immunogenicity of this protectant (Lee and Mooney 2012). Coating with alginate may require a calcium carbonate as a cross-linking agent (Colom et al. 2017). Another polymers used in this method are agarose (Bean et al. 2014), chitosan which shows muco-penetrative properties that may increase residence time in gastrointestinal tract (Bernkop-Schnürch et al. 1998; Takeuchi et al. 2005), or whey protein (Vonasek et al. 2014). Phages can also be encapsulated in synthetic polymers, like poly(lactic-*co*-glycolic acid) (PLGA) (Puapermpoonsiri et al. 2010), poly(*N*-isopropylacrylamide) (Hathaway et al. 2015), or polymethyl methacrylate (Stanford et al. 2010). Carrier which is encapsulating the phage to protect against storage conditions should also be chosen based on the form of phage application, for example, to help to deliver phage directly to the site of infection. Encapsulated phages released may be induced by polymer solvation (Korehei and Kadla 2014) or enzyme-driven degradation (Bean et al. 2014). Carriers may be also designed to respond to specific pH, like in gastrointestinal tract (McConnell et al. 2008; Stanford et al. 2010). To close emulsion in nanofibers, electrospinning is usually used. This method is based on drawing a charged solution of polymer and phage onto a grounded electrode during solvent evaporation (Korehei and Kadla 2013; Cheng et al. 2018). Protection of phages in this procedure may be provided by encapsulating them in fibers, like polyethylene oxide, cellulose diacetate (Korehei and Kadla 2014), or polyvinyl alcohol (Sarhan and Azzazy 2017).

Recently, some researchers are focusing on liposomes as a potential phage protectant, due to their high biocompatibility and ability to enhance stability and availability of carried particles (Torchilin 2005; Swaminathan and Ehrhardt 2012). Particular liposome features, like size, charge, lamellarity, and surface modifications, play a crucial role in stability and achieving phage destination (Eloy et al. 2014). Usually, liposome encapsulation is conducted by the thin-film hydration method (Angelova and Dimitrov 1986). It is based on dissolving lipids, like cholesterol and phosphatidylcholine, in organic solvent, usually chloroform, followed by evaporation of the solvent in a vacuum. In the next step, created film is rehydrated, causing formation of multilamellar liposomes (Colom et al. 2017). Liposomes may be manipulated by extrusion through porous membranes to achieve smaller size (Nieth et al. 2015; Zhang 2017). For creation of giant unilamellar vesicles (GUV), electroformation (Angelova et al. 2018) can be used, as well as rapid solvent exchange (Buboltz and Feigenson 1999) or gel-assisted formation which is based on rehydrating of film on polyvinyl alcohol gels instead of using rehydratation buffer (Weinberger et al. 2013). Liposomes with addition of charge inducer, for example, stearylamine, may protect against liposome aggregation and increase interaction with the mucus, improving potential for intestinal infection treatment (Hua et al. 2015; Singla et al. 2016). Moreover, functioning of liposomes may be expanded by modifications, like adding specific ligands (e.g., antibodies) for targeted delivery (Koning et al. 2002), polymers with hydrophilic properties to increase phage preparation circulation (Wang et al. 2013), or markers for tracking the liposomes (Urakami et al. 2009).

Isolated phages can also be immobilized on different kinds of surfaces, for protection against biofilm formation on medical devices, or antimicrobial dressing for biomedical use (Nogueira et al. 2017; Maszewska et al. 2018). Virus particles may be immobilized by passive adsorption. This process may cause a poor orientation of phage tails needed to interact with pathogen cells decreasing phage activity (Bennett et al. 1997). In other studies, phages were immobilized by chemical biotinylation on streptavidin-coated surfaces (Gervais et al. 2007) or covalent attaching on polyethylene and polyhydroxyalkanoate surface (Pearson et al. 2013; Wang et al. 2016), getting proper orientation of phage particles.

2.4.5 Phage Administration

Phage preparations for therapy purpose contain either only one phage or a mixture of phages in the form of a cocktail. The latter type may prevent from cross-resistance leaving bacteria resistant to one phage sensitive to another. For cocktail preparation, employment of phages using different receptors for binding a host is suggested (Gill and Hyman 2010).

The route of phage product administration depends strongly on the site of infection. For fighting pulmonary infection, phages may be administrated by nebulization of aerosol (Borie et al. 2009; Cooper et al. 2013). Gastrointestinal tract infections may be treated by oral application of phages using tablets or liquid solution (Sulakvelidze et al. 2001) or by rectal application (Sheng et al. 2006; Rozema et al. 2009; Wang et al. 2017a, b). For dermatological purposes, phages can be administered in the form of cream, lotions, or ointments (Brown et al. 2016,

2018). Phage particles may be applied directly in the wound through injection into the wound (McVay et al. 2007; Chhibber et al. 2018) or soaked bandages (Miao et al. 2011; Sarhan and Azzazy 2017). Nowadays, phages are also considered as an antibacterial agent in dental infections to treat caries and infection of root canal. For this purpose, usage of mouth wash, mouth rinse, topical gel, toothpaste, tooth powder, and slow-release implant would be proper ways of phage application (Norris 1990; Delisle 2004). Moreover, different products may occur in the form of nasal and ear drops or throat, fistulas and abscesses rinses to fight local infections.

2.5 Phage-Based Products Against Pathogenic Bacteria in Food

Year 2006 was a crucial year in the history of the use of bacteriophages in prevention of bacterial diseases. The US Food and Drug Administration and US Department of Agriculture have approved several bacteriophage products to be used for food protection against *Listeria monocytogenes*. LMP-102 (now ListShield™, Intralytix Inc.) was approved for treating of poultry and meat products, while LISTEX (Micreos) was approved to be used on cheese. A year later the same product was approved for use in all food products (US FDA/CFSAN: Agency Response Letters No. 000198 and No. 000298). Since then Intralytix has come up with two phage preparations targeting *L. monocytogenes*: ListShield™ and ListPhage™. ListPhage™ is an antimicrobial preparation for controlling *L. monocytogenes* in pet food (Intralytix Inc. ListPhage™ product description), while ListShield™ is designed to protect food products such as meat, poultry, cheese, and processed and fresh fruits and vegetables against *L. monocytogenes* contamination (Intralytix Inc. ListShield™ product description). Another product, designed to fight against *L. monocytogenes* in food, is already mentioned above, LISTEX (Micreos).

Studies addressing the effectiveness of phage-based products in reducing *L. monocytogenes* on food ready-to-eat beef and turkey showed that the presence of phage resulted in lower *L. monocytogenes* numbers of about 2 log CFU/cm^2 over a 28-day storage period at 4 °C in comparison to an untreated control. In this study, sliced meat cores stored at 4 and 10 °C were inoculated with *L. monocytogenes* to result in a surface contamination level of 10^3 CFU/cm^2. Phage preparation was then applied at 10^7 PFU/cm^2, and samples were taken at regular time intervals during product's shelf-life to enumerate viable *L. monocytogenes*. For meat stored at 10 °C, cell numbers of phage-treated samples remained below those of the untreated control only during the first 14 days of the experiment. The experiments also showed that phage can be used in combination with chemical antimicrobials to enhance the safety of meats and other food products (Chibeu et al. 2013). Other studies determined that LISTEX™ solution was able to reduce *L. monocytogenes* by 1.5–3 log within 24 h after applications in case of use on salmon fillets (Soni and Nannapaneni 2010) and sashimi (Migueis et al. 2017). Silva et al. (2014a) showed that the treatment with phage (8.3×10^7 PFU/g)-contaminated (10^5 CFU/g) cheeses caused an immediate drop in bacterial CFU by 2 log units compared to the control. However, after 7 days under refrigeration, bacterial reduction reached approximately 1 log unit. The

statistical analysis showed a significant difference ($p < 0.05$) between treated samples (at both 0 and 7 days) and control (Silva et al. 2014a). Furthermore, LISTEX™ is claimed to reduce *L. monocytogenes* up to 2 log in frozen vegetables (carrots) if contamination occurs before freezing and in the case of contamination happening after defrosting (carrots and beans) (Micreos Food Safety BV, LISTEX™ product description and data sheet).

After successful introduction of phage preparations for food protection to market, the number of products available is growing. Preparations against *Salmonella enterica* and *Escherichia coli* soon followed first preparations against *L. monocytogenes*.

There are currently three phage-based products for food protection against *Salmonella enterica* currently available on the market. SalmoFresh™ and SalmoLyse® are preparations produced by Intralytix Inc. SalmoFresh™ is designed to protect meat, especially poultry, sea food, fish, fruits, vegetables, and packed food from *S. enterica* contamination. Producers declare that phages contained in this preparation are active against the following serovars of *S. enterica*: Typhimurium, Enteritidis, Heidelberg, Newport, Hadar, Thompson, Kentucky, Georgia, Grampian, Agona, Senftenberg, Alachua, Infantis, Reading, and Schwarzengrund. The product has been approved to use in the USA, Canada, and Israel (Intralytix Inc. SalmoFresh™ product description). SalmoLyse® is used for controlling *Salmonella enterica* in pet food. It contains six phages that are able to infect the same *S. enterica* serovars as SalmoFresh™ (Intralytix Inc. SalmoLyse™ product description). The study by Heyse et al. (2015) showed that the cocktail was able to lyse 930 *Salmonella enterica* strains representing 44 serovars. In experiments involving dried pet food, it showed that treatment (dose $\geq 2.5 \pm 1.5 \times 10^6$ PFU/g) of feed after its contamination with various *S. enterica* serovars was able to reduce the count of *Salmonella* within 60 min (Heyse et al. 2015). Another study showed that raw pet food ingredients (like chicken, tuna, or turkey) treated with two concentrations of SalmoLyse® ($2–4 \times 10^6$ PFU/g and 9×10^6 PFU/g) showed significantly reduced (up to 92%) *Salmonella* contamination in comparison to control experiments. It was also determined that no side effects were observed in cats and dogs eating phage-treated food (Soffer et al. 2016). Salmonellex™ is produced by European-based company Micreos. It has been approved for clean label processing in the USA, EU, Canada, Australia, New Zealand, Israel, and Switzerland. The producers claim it reduces number of pathogens by 1–3 log (Micreos Food Safety BV, Salmonellex™ product description). Yeh et al. (2018) compared the effectivity of phage preparation (at final concentration of 10^9 PFU/ml), UV light, and organic acids on *Salmonella* populations in ground beef. The study determined that individual applications of phage preparation and UV light decreased *Salmonella* population approximately 1 log CFU/g, while combined applications of phage and UV provided a decrease of 2 log CFU/g (Yeh et al. 2018). This study suggests that in order to increase effectivity of phages, a combine treatment of food should be applied.

One of the main products against *Escherichia coli* is EcoShield™ (Intralytix Inc.). It is a commercially available product (approved by the FDA in 2011), composed of three lytic phages active against pathogenic strains of *E. coli* O157: H7. EcoShield™ is designed to protect various foods, including ground beef and

lettuce (Intralytix Inc. EcoShield ™ product description). Some studies showed that application of this phage mixture has proved to eliminate from 94 to 100% of *E. coli* O157:H7 and 87% in lettuce after a 5-min contact time (Carter et al. 2012; Sillankorva et al. 2012). Carter et al. (2012) demonstrated that EcoShield™ was a very effective product against *E. coli* O157:H7, but it did not protect food from recontamination.

Finalyse (Passport Food Safety Solutions) is another phage-based product specific for *E. coli* O157:H7 and other STEC pathogens. Finalyse is a mixture of naturally occurring phages, and it is sprayed on cattle to effectively reduce *E. coli* levels prior to entering the beef packing facility (Sillankorva et al. 2012). The producers claim it reduces the number of pathogens by $\geq$1 log after 1-h phage incubation (Passport Food Safety Solutions, Finalyse product description).

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