J. Microbiol. Biotechnol. (2017), 27(12), 2075–2088
https://doi.org/10.4014/jmb.1710.10049

Review

jmb

Recent Trends in *Salmonella* Outbreaks and Emerging Technology for Biocontrol of *Salmonella* Using Phages in Foods: A Review

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Received: October 30, 2017
Accepted: November 15, 2017

First published online
November 15, 2017

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pISSN 1017-7825, eISSN 1738-8872

Salmonella is one of the principal causes of foodborne outbreaks. As traditional control methods have shown less efficacy against emerging *Salmonella* serotypes or antimicrobial-resistant *Salmonella*, new approaches have been attempted. The use of lytic phages for the biocontrol of *Salmonella* in the food industry has become an attractive method owing to the many advantages offered by the use of phages as biocontrol agents. Phages are natural alternatives to traditional antimicrobial agents; they have proven effective in the control of bacterial pathogens in the food industry, which has led to the development of different phage products. The treatment with specific phages in the food industry can prevent the decay of products and the spread of bacterial diseases, and ultimately promotes safe environments for animal and plant food production, processing, and handling. After an extensive investigation of the current literature, this review focuses predominantly on the efficacy of phages for the successful control of *Salmonella* spp. in foods. This review also addresses the current knowledge on the pathogenic characteristics of *Salmonella*, the prevalence of emerging *Salmonella* outbreaks, the isolation and characterization of *Salmonella*-specific phages, the effectiveness of *Salmonella*-specific phages as biocontrol agents, and the prospective use of *Salmonella*-specific phages in the food industry.

Keywords: Phages, *Salmonella*, biocontrol, outbreaks

Introduction

Salmonella is one of the major foodborne pathogens and public health concerns in industrialized and underdeveloped countries, where it accounts for 93.8 million cases of foodborne illness and 155,000 deaths per year [1]. In the USA, *Salmonella* infection accounts for approximately 1.5 million infections each year, an incidence rate of 17.6 cases per 100,000 population, the largest death rate (39%) among all foodborne pathogens, and more than $3.6 billion of medical care costs required for treatment in 2014 [2, 3]. The contamination of *Salmonella* can occur at any point on the farm-to-consumer continuum, such as production, harvest, processing, storage, transportation, retailing, and handling at home [4, 5].

In 1996, to reduce the risk of *Salmonella* contamination, the Food Safety and Inspection Service of the USDA established new requirements to modernize poultry and meat facilities to reduce the occurrence and number of foodborne pathogens. In addition, the FDA established a guideline for fresh produce ("Guide to Minimize Microbial Food Safety Hazards for Fresh Fruits and Vegetables") in 1998. These improved hygiene practices have reduced the likelihood of *Salmonella* contamination during food preproduction; however, it is a problem that will never be fully eliminated [6]. The introduction of antimicrobial agents, which are defined as chemicals, drugs, or substances that can reduce or eliminate the microorganisms, has been considered as the most effective intervention strategy to decrease *Salmonella* contamination. However, the continuous use of antimicrobial agents has yielded several negative effects, such as antibiotic residues in food products and the emergence of multidrug-resistant *Salmonella* strains, such as *Salmonella* Typhimurium DT104 [7].

A new eco-friendly intervention strategy is therefore required for use as a biocontrol agent against *Salmonella* [8]. In recent years, phages have received new attention owing to their promising characteristics, such as target specificity without damage to coexisting microflora, inherent low toxicity, robustness to harsh environments, widespread distribution, self-replication, and relatively cheap and easy production [9–12]. Indeed, phages can serve (i) therapeutic purposes (reduction of pathogens in animals); (ii) sanitation purposes (disinfection of food contact surfaces and equipment); (iii) as biocontrol agents (reduction of pathogens in foods); and (iv) as biorecognition elements (detection of pathogens as biosensing elements in detection devices) [8, 11].

Although some reviews have highlighted the importance of the general introduction of phages into foods and the applications of phages in food safety, few reports have addressed the use of phages for the specific control of *Salmonella* in foods. Thus, this review aims to elucidate the use of *Salmonella*-specific phages as biocontrol agents for *Salmonella* in foods. The scope of this review encompasses the pathogenic characteristics of *Salmonella*, current emergence and persistence of *Salmonella* outbreaks, isolation and characterization of *Salmonella*-specific phages, employment of *Salmonella*-specific phages in foods as biocontrol agents, and the prospective use of *Salmonella*-specific phages in the food industry.

General Characteristics of *Salmonella*

Salmonella is a gram-negative, rod-shaped, motile (with the exception of *S.* Gallinarum and *S.* Pullorum), mesophilic, and facultative anaerobe that belongs to the family Enterobacteriaceae [13, 14]. Since the first discovery of *Salmonella* from pigs by Theobald Smith in 1855, more than 2,600 serotypes have been identified and reported. Owing to the far-reaching diversity within the genus *Salmonella*, the Centers for Disease Control and Prevention (CDC) recommend use of the nomenclature system proposed by the World Health Organization Collaborating Centre, despite the ongoing controversy [15].

The majority of *Salmonella* infections (also called salmonellosis) are caused by the consumption of foods contaminated with *Salmonella* species. The symptoms of salmonellosis may include diarrhea, fever, abdominal cramps, nausea, occasional vomiting, and headache, and usually occur 12–72 h after consumption and last for 4–7 days [16, 17]. The infection is usually self-limiting, as there is no further penetration of the lamina propria of epithelial cells; therefore, antimicrobial interventions, such as ampicillin, gentamicin, trimethoprim/sulfamethoxazole, or ciprofloxacin, are generally unnecessary in most cases of *Salmonella* infection [1, 18]. However, these antimicrobial interventions are necessary in cases in which the pathogen is severely virulent to certain susceptible groups, including children under 5 years of age, the elderly, and patients who are immunocompromised [19, 20].

Recent Trends in *Salmonella* Outbreaks

Until two decades ago, reported *Salmonella* outbreaks predominantly involved chicken, turkey, pork, meat, and eggs [21]. Recently, *Salmonella* outbreaks have occurred in a wider range of foods, as summarized in Table 1. The traditionally common foods in which *Salmonella* outbreaks occur, such as chicken, beef, turkey, pork, and eggs, were still a prominent component of *Salmonella* outbreaks (5,066/11,921). However, the number of outbreaks of *Salmonella* infection associated with fresh produce has recently experienced a marked increase. Compared with 2008, the number of outbreaks associated with fresh produce increased almost 4.3-fold in 2017. The major sources of outbreaks from fresh produce include alfalfa sprouts, cantaloupes, mangoes, cucumbers, bean sprouts, and papayas. The most unexpected finding was the occurance of *Salmonella* outbreaks even in dried foods, such as peanut butter, chia powder, nut butter, seeds, and pistachios since 2007. As the consumption of fresh fruits and vegetables is become increasingly popular owing to the trend for healthy foods and diets, the impact of *Salmonella* outbreaks from fresh produce will increase [22–28].

More importantly, most fresh produce undergo minimal processing (cutting, peeling, and slicing); often, fresh produce is usually consumed raw. After contamination during processing, it is hard to kill or reduce *Salmonella* contamination in fresh produce prior to consumption. Thus, the contamination of *Salmonella* in fresh produce should be controlled at the early stages of production. In addition, *Salmonella* outbreaks associated with poultry, meat, and egg products still pose problems, despite the various intervention strategies and efforts. Therefore, a new intervention strategy should be developed to manage the new trends in *Salmonella* outbreaks.

Major *Salmonella* Serotypes Associated with Outbreaks

The 20 *Salmonella* serotypes most frequently reported to

Table 1. Multi-state outbreaks associated with *Salmonella* in the USA (2010-2017) (Source: CDC website).

Year	Serovar	Food	State	Case	Death	Hospitalization	Remarks
2017	*S*. Urbana	Papayas from Mexico	3	7	0	4	-
	S. Anatum	Papayas from Mexico	3	14	1	5	-
	S. Newport, *S*. Infantis	Papayas from Mexico	4	4	0	2	*S*. Newport (3)[a], *S*. Infantis (1)
	S. Thompson, *S*. Kiambu, *S*. Agona, *S*. Gaminara	Papayas from Mexico	24	210	1	67	*S*. Thompson (135), *S*. Kiambu (59), *S*. Agona (10), *S*. Gaminara (6)
2016	*S*. Oranienburg	Egg shells	3	8	0	2	-
	S. Reading, *S*. Abony	Alfalfa sprouts	9	36	0	7	*S*. Reading (30), *S*. Abony (1), both (5)
	S. Montevideo, *S*. Senftenberg	Pistachios	9	11	0	2	*S*. Montevideo (9), *S*. Senftenberg (2)
	S. Muenchen, *S*. Kentucky	Seed lot	12	26	0	8	*S*. Muenchen (25), *S*. Kentucky (1)
	S. Virchow	Raw meal product	23	33	0	6	-
2015	*S*. Paratyphi B, *S*. Poona	Nut butter spreads	10	13	0	0	-
		Cucumbers from Mexico	40	907	6	204	Six deaths were reported in Arizona (1), California (3), Oklahoma (1), and Texas (1).
	S. I 4,[5],12:I:-, *S*. Infantis	Pork	5	192	0	30	*S*. I 4,[5],12:I:- (188), *S*. Infantis (4)
	S. Enteritidis	Raw, frozen, stuffed chicken entrees	1	5	0	2	-
	S. Enteritidis	Raw, frozen, stuffed chicken entrees	7	15	0	4	-
	S. Paratyphi B	Frozen raw tuna	11	65	0	11	-
2014	*S*. Enteritidis	Bean sprouts	12	115	0	28	-
	S. Braenderup	Nut butter	5	6	0	1	-
	S. Newport, *S*. Hartford, *S*. Oranienburg	Chia powder	16	31	0	5	*S*. Newport (20), *S*. Hartford (7), *S*. Oranienburg (4)
	S. Heidelberg	Separated chicken	1	9	0	2	-
	S. Stanley	Cashew cheese	3	17	0	3	-
2013	*S*. Heidelberg	Chicken	29	634	0	241	
	S. Montevideo, *S*. Mbandaka	Sesame paste	9	16	1	1	-
	S. Saintpaul	Cucumbers from Mexico	18	84	0	17	-
	S. Heidelberg	Chicken	13	134	0	33	-
	S. Typhimurium	Ground beef	6	22	0	7	-
2012	*S*. Bredeney	Peanut butter	20	42	1	10	-
	S. Braenderup	Mangoes	15	127	0	33	-
	S. Typhimurium, *S*. Newport	Cantaloupe	24	261	3	94	*S*. Typhimurium (228), *S*. Newport (33)
	S. Enteritidis	Ground beef	9	46	0	12	-
	S. Bareilly and *S*. Nchanga	Raw scraped ground tuna	28	425	0	55	*S*. Bareilly (410), *S*. Nchanga (15)
2011	*S*. Enteritidis	Restaurant chain A	10	68	0	21	-
	S. Typhimurium	Ground beef	7	20	0	8	-
	S. Enteritidis	Turkish pine nuts	5	43	0	2	-
	S. Heidelberg	Ground turkey	34	136	1	37	-
	S. Agona	Papayas from Mexico	25	106	0	10	-
	S. Heidelberg	Boiled chicken livers	8	190	0	30	-
	S. Panama	Cantaloupe	10	20	0	3	-
	S. Enteritidis	Alfalfa sprouts and Spicy sprouts	25	5	0	3	-
	S. Hadar	Turkey burgers	12	10	0	3	-

Table 1. Continued.

Year	Serovar	Food	State	Case	Death	Hospitalization	Remarks
2010	*S.* I4,[5],12:I:-	Alfalfa sprouts	26	140	0	33	-
	S. Enteritidis	Egg shells		3,578			-
	S. Chester	Cheesy chicken rice frozen entrée	18	44	0	16	-
	S. Typhi	Frozen mamey fruit pulp		9			-
	S. Hartford, *S.* Baildon	Mexican restaurant chain	21	155	0	42	*S.* Hartford (80), *S.* Baildon (75)
	S. Montevideo	Italian-style meats	44	272	0	52	-
2009	*S.* Saintpaul	Alfalfa sprouts	14	235	0	7	-
	S. Typhimurium	Peanut butter	46	714	9	171	
2008	*S.* Saintpaul	Peppers	43	1,442	2	286	Occurred in the USA and Canada
	S. Agona	Rice and wheat cereals	16	28	0	8	-
	S. Lichfield	Cantaloupes	16	51	0	16	-
2007	*S.* I4,[5],12:i:-	Pot pies	35	272	0	65	-
	S. Wandsworth	Vegetable-flavored rice and corn snack	20	65	0	6	-
	S. Tennessee	Peanut butter	44	425	0	71	-
2006	*S.* Typhimurium	Tomatoes	21	183	0	22	-
	S. Oranienburg	-	10	41	0	7	Occurred in the USA and Canada
2005	*S.* Braenderup, *S.* Newport	Tomatoes	21	154	0	26	*S.* Braenderup (82), *S.* Newport (72)

[a]The number of cases is given in parentheses.

the US CDC in 2003, 2008, and 2013 are presented in Table 2. Although each year differed slightly, these 20 serotypes accounted for approximately 68.8% of the total number of *Salmonella* outbreaks. Among them, *S.* Enteritidis and *S.* Typhimurium accounted for 27.9%, followed by *S.* Newport, *S.* I 4,[5],12:I:- (variant of *S.* Typhimurium), *S.* Javiana, and *S.* Heidelberg. A CDC study from 2006 reported *S.* Typhimurium (20%), *S.* Enteritidis (15%), *S.* Newport (10%), *S.* Javiana (7%), and *S.* Heidelberg (5%), which together accounted for approximately 56% of all *Salmonella* infections, as the major serotypes of *Salmonella*.

S. I 4,[5],12:I:- was one of the top major serotypes of *Salmonella* outbreaks in the last two decades. In addition, other *Salmonella* serotypes (not indicated in Table 2) have been recently reported as a cause of *Salmonella* outbreaks; these include *S.* Abony, *S.* Anatum, *S.* Baildon, *S.* Bredeney, *S.* Chester, *S.* Gaminara, *S.* Hartford, *S.* Kentucky, *S.* Kiambu, *S.* Mbandaka, *S.* Nchanga, *S.* Reading, *S.* Senftenberg, *S.* Stanley,

Table 2. Comparison of the 20 *Salmonella* serotypes most frequently reported to the CDC in 2003, 2008, and 2013.

Serotype	Rank			Serotype	Rank		
	2003	2008	2013		2003	2008	2013
S. Enteritidis	2	1	1	*S.* Braenderup	11	10	11
S. Typhimurium	1	2	2	*S.* Oranienburg	9	11	12
S. Newport	3	3	3	*S.* Thompson	14	18	13
S. I 4,[5],12:i:-	12	8	4	*S.* Mississippi	15	17	14
S. Javiana	5	4	5	*S.* Agona	13	13	15
S. Heidelberg	4	6	6	*S.* Typhi	16	15	16
S. Infantis	10	12	7	*S.* Bareilly	19	23	17
S. Saintpaul	7	5	8	*S.* Paratyphi B	17	16	18
S. Muenchen	8	9	9	*S.* Poona	22	14	19
S. Montevideo	6	7	10	*S.* Berta	23	29	20

S. Virchow, and *S*. Urbana. The important point indicated in Table 2 is that several *Salmonella* serotypes are known as multidrug-resistant strains, including *S*. Agona, *S*. Anatum, *S*. Pullorum, *S*. Schwarzengrund, *S*. Choleraesuis, *S*. Derby, *S*. Dublin, *S*. Heidelberg, *S*. Kentucky, *S*. Newport, *S*. Senfenberg, *S*. Typhimurium, and *S*. Uganda [29, 30]. Given the prevalence of emerging *Salmonella* serotypes, new methods to control these *Salmonella* serotypes in food should be developed. One of the most promising methods for the control of emerging *Salmonella* serotypes in various foods is to deploy phages in food systems as biocontrol agents. Phages have attracted attention owing to their capability to lyse and inhibit *Salmonella*, as well as other pathogens, in foods and food environments.

Phages

Phages (also called bacteriophages) are virus particles that specifically infect bacteria, and are the most abundant entities (10^{31}–10^{32}) in nature [31–33]. To develop a better understanding of the interaction between phages and their host *Salmonella*, different types of phages, with their own unique life cycles, will be focused on in this review rather than an introduction of the general characteristics of phages, which are available in other review papers [11, 34, 35].

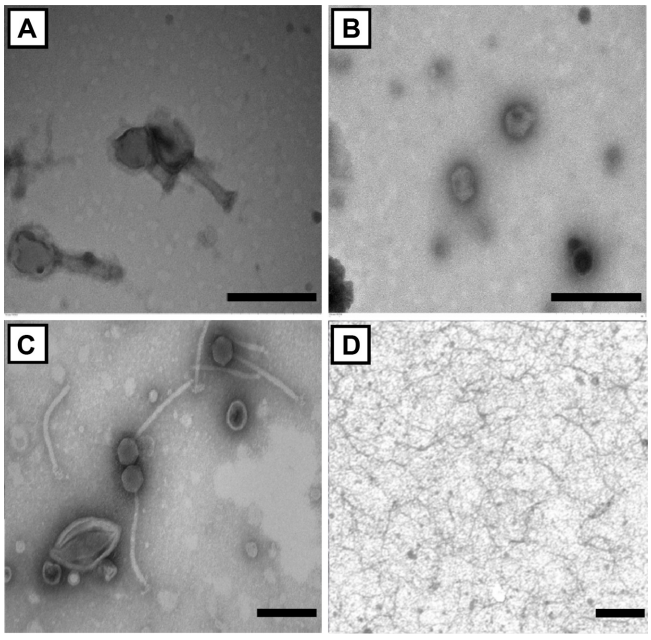

Fig. 1. TEM images of (**A**) *Yersinia enterocolitica*-specific phage, *Myoviridae*; (**B**) *Shigella sonnei*-specific phage, *Podoviridae*; (**C**) *Aeromonas hydrophila*-specific phage, *Siphoviridae*; and (**D**) *Salmonella* Typhimurium-specific phage, filamentous type [85]. All scale bars are 200 nm.

Phages consist of either DNA or RNA and a polyhedral capsid protein (except for filamentous phages) (Fig. 1) [35, 36]. Their capsid proteins are attached to a tail connected with fibers used for attachment to the target bacteria. When the phages bind specificaaly to the bacterial surface, they can undergo replication via two possible pathways: the lytic pathway, or the lysogenic pathway. Lytic phages (virulent phages) integrate their DNA into bacterial chromosome to produce the prophage, which is replicated by using the replication machinery of the host, and the phages are finally released by the lysis of their hosts. In contrast, lysogenic phages (temperate phages) integrate into their host genome or exist as plasmids within their host bacteria, instead of inducing the lysis of the host bacteria [37–39]. However, bacterial lysis as a result of lysogenic phages can be initiated by environmental stimulus [40]. In addition, there is one more pathway available, which is called the pseudolysogenic pathway. Pseudolysogenic phages also enter the host bacteria; however, they stay or do not integrate until the occurrence of a specific condition, which triggers selection of the lytic or lysogenic pathway [37, 41]. Among the different types of phages, lytic phages have been isolated and purified from the environment and foods wherever a host is available. The isolation of phages against the target bacteria led to extensive attempts to control foodborne pathogens owing to the ability of bacterial lysis [11, 42]. Therefore, the search for new and strong lytic phages is a requirement for the use of phages as biocontrol agents in food systems.

Salmonella-Specific Phages: Isolation and Morphological Characterization

Phages have been investigated owing to their role as biocontrol agents for the improvement of food safety [11, 43]. At present, several thousands of phages against various targets have been isolated from various environments and foods [11, 32]. Approximately 96% of these isolated phages were tailed and lytic phages in one of three families: *Myoviridae* (24.5%), *Siphoviridae* (61%), and *Podoviridae* (14%), in the order *Caudovirale* [44]. The isolated and purified *Salmonella*-specific phages published in scientific research articles since 1982 are presented in Table 3. The majority of isolated *Salmonella*-specific phages were against *S*. Typhimurium (approximately 59%), followed by *S*. Enteritidis (approximately 26%). The explanation for the predominance of these two phages is presumably because these two pathogens are the most problematic and ubiquitous

Table 3. *Salmonella*-specific phages reported in scientific research articles (1982–2017).

Target	Phage name	Classification	Morphology		Stability		DNA size (kb)	References
			Head length	Tail length	pH	Temp. (°C)		
Salmonella spp. (*N* = 3)	FGCSSa1	*Myoviridae*	107.0 nm	123.0 nm	-	-	-	[63]
	FGCSSa2	*Siphoviridae*	66.0 nm	112.0 nm	-	-	-	[63]
	SS3e	*Siphoviridae*	-	-	-	-	40.8	[64]
S. Enteritidis (*N* = 9)	ϕSP-1	*Podoviridae*	-	-	5–8	37–40	86.0	[65]
	PA13076	*Myoviridae*	66.0 nm	90.0 nm	6–11	30–50	-	[8]
	PC2184	*Myoviridae*	65.0 nm	106.0 nm	5–11	30–50	-	[8]
	SEA1	*Myoviridae*	110.0 nm	100.0 nm	-	-	190.0	[31]
	SEA2	*Myoviridae*	110.0 nm	100.0 nm	-	-	170.0	[31]
	PVP-SE1	*Myoviridae*	84.0 nm	120.0 nm	-	-	146.0	[66]
	SE2	*Siphoviridae*	68.0 nm	110.0 nm	4–9	-	-	[67]
	vB_SenS-Ent1	*Siphoviridae*	64.0 nm	116.0 nm	-	-	42.4	[68]
	SETP 12	*Siphoviridae*	62.5 nm	120.0 nm	-	-	42.0	[69]
S. Pullorum (*N* = 2)	PSPu-4-116	*Myoviridae*	74.3 nm	114.2 nm	6–9	30–60	45.2	[70]
	PSPu-95	*Siphoviridae*	57.1 nm	103.6 nm	6–9	30–60	58.3	[70]
S. Typhimurium (*N* = 20)	SFP10	*Myoviridae*	68.7 nm	131.3 nm	4–10	20–60	158.0	[71]
	SPN3US	*Myoviridae*	-	-	-	-	240.4	[72]
	Vi phage E1	*Myoviridae*	55.0 nm	205.0 nm	-	-	45.4	[73]
	Fels2	*Myoviridae*	55.0 nm	110.0 nm	-	-	-	[74]
	SPN9CC	*Podoviridae*	-	-	-	-	40.1	[75]
	phiSE7	*Podoviridae*	43.0 nm	12.0 nm	-	-	-	[17]
	fmb-p1	*Siphoviridae*	57.2 nm	171.2 nm	4–11	4–70	43.3	[76]
	ϕSTIz1	*Siphoviridae*	52.9 nm	190.3 nm	4–11	4–60	-	[77]
	SSA1	*Siphoviridae*	-	-	-	-	125.0	[31]
	STA2	*Siphoviridae*	-	-	-	-	145.0	[31]
	STA3	*Siphoviridae*	-	-	-	-	45.0	[31]
	STA9	*Siphoviridae*	-	-	-	-	-	[31]
	SSU5	*Siphoviridae*	70.0 nm	220.0 nm	-	-	103.2	[78]
	phSE-1	*Siphoviridae*	67.0 nm	152 nm	-	-		[79]
	phSE-2	*Siphoviride*	67.0 nm	177.0 nm	-	-	49	[79]
	phSE-5	*Shphoviridae*	67.0 nm	160.0 nm	-	-	49	[79]
	MB78	*Siphoviridae*	30.0 nm	90.0 nm	-	-	-	[80]
	P164L1	*Siphoviridae*	73.0 nm	178.0 nm	-	-	-	[81]

The dash (-) indicates that the data were not provided from their own research article.

serotypes of *Salmonella*, as indicated in Tables 1 and 2.

The morphological characteristics and stability of phages determined from the available literature are also presented in Table 3. All *Salmonella*-specific phages in Table 3 are tail and lytic phages and organized into *Myoviridae* (12/34), *Siphoviridae* (19/34), and *Podoviridae* (3/34), which correlated with the aforementioned data. Based on the International Committee on Taxonomy of Viruses, *Podoviridae* has a short and noncontractile tail, whereas *Siphoviridae* has a relatively long and noncontractile tail. However, as *Myoviridae* has a contractile tail, the length of tail was not a determinant factor for their categorization [44]. As shown in Fig. 1, the morphology of tailed phages is completely different from the morphology of filamentous phages, a type of lysogenic phage (Fig. 1D). However, the lengths of the tail and the heads are very diverse, so it is difficult to differentiate between *Siphoviridae* and *Myoviridae* by using only their tail and head lengths. For example, the tail length of phiSE7

classified as *Podoviridae* was much smaller than any other any *Salmonella*-specific phages, even its head length. The isolation and characterization of *Salmonella*-specific phages can provide secure background information for use as biocontrol agents for the control of emerging *Salmonella* serotypes.

Biocontrol of *Salmonella* Using Phages as Biocontrol Agents in Foods

The biocontrol effectiveness of phages is often determined by the multiplicity of infection (MOI). The MOI is defined as the average number of phages available to infect a single bacterium; a lower MOI is more beneficial and economical for use in the food industry. Phage applications have been reported to successfully reduce the numbers of *Salmonella* in various foods and food products [40, 45–49]. The specific foods and food products that use phages as biocontrol agents to inhibit specific *Salmonella* serotypes include cheddar cheese made from raw and pasteurized milk [49], chicken frankfurters [48], pig skin [47], chicken breasts [40, 46], romaine lettuce [45], energy drinks, whole and skimmed milk [8], apple juice [50], alfalfa seeds [51], and sprouts [25]. A comprehensive summary of the current applications of phages to control *Salmonella* species in various foods is presented in Table 4.

Many phages specific to *Salmonella* spp. were investigated for the effective reduction of the growth of *Salmonella* spp. on a variety of fresh and fresh-cut produce [26]. A 1.37 Log reduction of *Salmonella* growth was achieved by using only phage-A on mustard seeds, whereas the combination of phage-A and phage-B resulted in a 1.50 Log reduction in CFU of *Salmonella* growth in the soaking water of broccoli seeds [48]. The application of a biocontrol mixture, including *Enterobacter asburiae* JX1 and a cocktail of phages, on tomatoes resulted in a reduction of the *Salmonella* persistence to 2% (1 of 57 positive), although no synergistic action was found between *E. asburiae* JX1 and the bacteriophage cocktail [52]. Two *Salmonella* phages, SSP5 and SSP6, were used by Kocharunchitt *et al.* [51] to control *Salmonella* Oranienburg on alfalfa seeds, as chemical disinfectants were unsatisfactory. The possible explanations include changes in the environment or host cells, or high levels of background microbiota on the seeds, which may offer alternative phage attachment sites. Fresh-cut romaine lettuces that were contaminated with *Salmonella enterica* serovars Enteritidis and Typhimurium were also tested by Spricigo *et al.* [45]. The phage cocktail significantly reduced the *Salmonella* concentration. Leverentz *et al.* [34] investigated lytic phages for the control of *Salmonella enterica* Enteritidis populations in fresh-cut melons and apples. It was found that phages were only able to significantly reduce the *Salmonella* populations in melon slices. Oliveira *et al.* [53] isolated a total of 112 putative antagonist isolates for the inhibition of the growth of *Salmonella enterica* on lettuce disks. Five different genera reduced *Salmonella enterica* growth by more than 1 Log unit at 20°C at the end of 3 days. The M309 strain was selected for test on lettuce disks at 10°C against *Salmonella enterica*, *E. coli* O157:H7, and *Listeria monocytogenes*, and was able to reduce the *Salmonella enterica* and *E. coli* O157:H7 populations. However, the addition of phages such as Listex P100 and Salmonelex alone did not result in a significant reduction of the *Salmonella* populations. The authors concluded that biocontrol using phages possessed potential effects; however, combination effects with other technologies may be required to improve their application in fresh-cut lettuce.

As the application of phages alone to produce was not significantly effective, many researchers investigated the effects of a combination of phages with other antimicrobials [25, 46, 54, 55]. Ye *et al.* [25] investigated the biocontrol of *Salmonella* on sprouting mung bean and alfalfa seeds by using lytic phages, together with the *Enterobacter asburiae* JX1 strain, which exhibits antagonistic activity against *Salmonella*. The combined treatment significantly inhibited the growth of *Salmonella* spp. on mung bean sprouts and alfalfa sprouting seeds, reducing the number of *Salmonella* cells on alfalfa sprouts to below the detectable level. The combined activity of *Enterobacter asburiae* JX1 and a lytic phage cocktail against *Salmonella* Javiana was evaluated on tomato fruits and plants by the same researchers [54]. The authors did not observe the synergistic activity of the *Enterobacter asburiae* JX1 strain and phage mixture on tomato fruits. Differences between the trials were thought to be from the various conditions of stored tomatoes and sprouting mung beans, including the temperature, incubation period, humidity, nutrient composition of sprouts and tomatoes, and the remnants of antimicrobial agents on the tomato surface. Magnone *et al.* [55] found that another type of combined treatment of fresh vegetables (phage application before storage at 10°C and a wash with levulinic acid after storage at 10°C) was more successful for the reduction of *Salmonella* count in cases in which one-step treatment did not yield satisfactory results.

The efficacy of phage application to animal meat products is expected to be superior to the live animals. This has led to extensive attempts to use phages in red meats and poultry products to reduce *Salmonella* infection [8, 45, 56].

Table 4. Phage applications to control *Salmonella* in foods and food products.

Target	Phage name	Food product	Result outline
S. Oranienburg	SSP5, SSP6	Alfalfa seeds	10^{-1} CFU/g reduction in viable *Salmonella* 3 h after phage application at 25°C [51].
Salmonella cocktail	Cocktail of six selected phages (F01, P01, P102, P700, P800, and FL 41)	Mung beans, alfalfa seeds	Combined treatment reduced the level of *Salmonella* by 6.7 Log CFU/g on sprouting mung beans after 4 days at room temperature. Similar results were obtained for alfalfa sprouts [25].
S. Javiana	Cocktail of five lytic phages	Red tomatoes	Combined treatment had a negligible impact on the final populations of the pathogen [54].
S. Enteritidis and *S.* Typhimurium	Cocktail of three lytic phages (UAB_Phi 20, UAB_Phi78, and UAB_Phi87)	Romaine lettuce	Phage cocktail reduced *Salmonella* Typhimurium and Enteritidis 3.9 Log CFU/g and 2.2 Log CFU/g in lettuce [45].
S. Enteritidis	SCPLX-1 (cocktail of four lytic phages)	Red Delicious apples, honeydew melons (slices)	Bacterial cells in melon slices at 5°C and 10°C were reduced to 3.5 Log CFU/g. No significant reduction was observed in apple slices [34].
S. Typhimurium	Cocktail of lytic phages	Undercooked poultry	*Salmonella*-specific phage treatment to poultry chicken reduced *S.* Typhimurium to 3 Log over 17 days. No significant change in *Salmonella* population was detected with less than 12 days of phage treatment [40].
Salmonella cocktail (*S.* Typhimurium, *S.* Paratyphi-C, *S.* Miami, *S.* Agona, and *S.* Anatum)	Lytic *Salmonella* phage fmb-p1	Fresh chilled pork	Phage reduced *Salmonella* number by more than 2 Log CFU/g on fresh chilled pork after 14 days at 4°C temperature [47].
S. Havana	Phage-A3CE	Raw, unprocessed chickens	More than 90% of *S.* Havana population in host was reduced 6 h after the phage application at room temperature [82].
Salmonella cocktail	Phage S16 and Felix-O1a (FO1a)	Ground meat and poultry	Phage treatment held at 4°C for 6 h (meat) and 30 min (poultry) reduced *Salmonella* significantly to 1 and 1.1 Log CFU/g from 7 Log CFU/g, respectively [22].
S. Typhimurium, *S.* Enteridis, and *S.* Heidelberg	*Salmonella* lytic phage (SalmoFresh)	Chicken breast fillets	The phage in combination with cetylpyridinium chloride and lauric arginate reduced *S.* Typhimurium, *S.* Enteritidis, and *S.* Heidelberg up to 5 Log units in vitro at 4°C [46].
S. Enteritidis	SE07	Fruit juice, fresh eggs, beef and chicken meat	The application of phage SE07 on food matrices (fruit juice, fresh eggs, beef and chicken meat) reduced *S.* Enteritidis population to about 2 Log cycles at 4°C for 48 h [56].
S. Enteritidis (SE) ATCC13076 and CVCC2184	Cocktail of two lytic phages, vB_SenM-PA13076 (PA13076) and vB_SenM-PC2184 (PC2184)	Chicken breast, pasteurized whole milk, and Chinese cabbage	Cocktail phage therapy on *Salmonella* reduced bacterial counts to 1.5–4 Log CFU/sample at 4°C for 5 h [8].
S. Enteritidis	SJ2	Processed food (raw and pasteurized cheese)	*Salmonella* Enteritidis survived in raw and pasteurized milk cheese without phage treatment (10^3 CFU/g after 99 days at 88°C). No counts of *S.* Enteritidis were found in pasteurized cheeses treated with phages [49].
S. Typhimurium DT104	Felix O1	Meat (chicken frankfurters)	Approximately 2 Log reduction of *S.* Typhimurium DT104 was achieved by the combined activity of clearer plaque phenotypes and wild-type Felix O1 on chicken frankfurters [48].
S. Typhimurium and *S.* Enteritidis	Phage (A and B)	Fresh produce (sprouting seeds)	A 1.37 Log reduction of *Salmonella* was reached by using only phage-A on mustard seeds, whereas the combination of phage-A and phage-B produced a 1.50 Log/CFU reduction of *Salmonella* in the broccoli seeds [50].
S. Enteritidis	PHL 4	Meat (broiler, turkey)	Phage treatments (PHL 4) at 10^{10} PFU/ml on *S.* Enteriditis reduced the level of *Salmonella* recovery as compared with controls [52].

Table 4. Continued.

Target	Phage name	Food product	Result outline
S. Typhimurium	P7	Meat (raw/cooked beef)	A 2–3 Log/CFU host bacteria was reduced at 5°C, while significant reduction of 6 Log/CFU was achieved at 24°C compared with phage-free controls [83].
S. Javiana	Phage cocktail	Fresh produce (tomatoes)	The application of biocontrol mixture of *Enterobacter asburiae* JX1 and cocktail phages on tomatoes reduced the *Salmonella* persistence to 2% (1 of 57 positive) and no synergistic action was found between *E. asburiae* JX1 and the phage cocktail [54]
S. Typhimurium U288	Pig skin	Phage cocktail	Phage cocktail treatment on pig skin reduced *S.* Typhimurium U288 from Log 4.7 CFU to Log 3.5 CFU [84]

Goode *et al.* [57] used phages to control *Salmonella enterica* serovar Enteritidis on chicken skin that had been inoculated with commercially relevant numbers of bacteria. The *Salmonella* phage (Felix-O1), which has a broad host range within the genus *Salmonella*, demonstrated a reduction of approximately 2 Log units in *Salmonella* Typhimurium DT104 in inoculated chicken frankfurters [48]. Bao *et al.* [8] used two lytic phages of vB_SenM-PA13076 (PA13076) and vB_SenM-PC2184 (PC2184) isolated from chicken sewage. The lytic abilities of these two phages in liquid culture showed an MOI of 10^4 to inhibit *Salmonella*, with PC2184 exhibiting greater activity than PA13076. A significant reduction in bacterial numbers (1.5–4 Log CFU/sample) was obtained in chicken breast. The inhibitory effect of phages was better at 4°C than at 25°C. Phages were also found to be effective in the reduction of the intestinal colonization by *Salmonella* spp. in chicken; depending on the phage type, a 2–4 Log reduction was observed [40, 58]. The efficacy of lytic phages for the reduction of *Salmonella* spp. on chicken skin has been studied and a 0.5–1.3 Log reduction was found to increase as the MOI increased [46].

The efficacy of phages can also be enhanced through the combination of phages with other microbial hurdles in animal food and food products. The major combinations include the use of phage cocktails and other antimicrobials in an attempt to increase the efficacy of the phage treatment [22, 45–47, 59]. Spricigo *et al.* [45] determined the effectiveness of three different lytic phage cocktails, UAB_Phi 20, UAB_Phi78, and UAB_Phi87, on the growth of *Salmonella enterica* serovar Typhimurium and *Salmonella enterica* serovar Enteritidis on pig skin, chicken breast, fresh eggs, and lettuce. A significant bacterial reduction (>4 and 2 Log/cm^2 for *Salmonella* Typhimurium and *Salmonella* Enteritidis, respectively) was obtained in pig skin sprayed with the bacteriophage cocktail and then incubated at 33°C for 6 h. Significant decreases in the concentration of *Salmonella* Typhimurium and *Salmonella* Enteritidis were also measured in chicken breasts dipped for 5 min in a solution containing the bacteriophage cocktail and then refrigerated at 4°C for 7 days (2.2 and 0.9 Log CFU/g, respectively). Yeh *et al.* [22] conducted a study on the effects of bacteriophage application during tumbling on *Salmonella* populations in ground meat and poultry. Red meat trim and poultry were inoculated with a *Salmonella* cocktail to give a contamination level of 7 Log CFU/g in ground products. A commercial preparation containing phages S16 and Felix-O1a (FO1a) was applied during tumbling at 10^7 and 10^8 PFU/ml. The samples were stored at 4°C for 6 or 18 h (red meat) and 30 min or 6 h (poultry). Overall, the phage application on the trim resulted in a reduction of 1 and 0.8 Log CFU/g of *Salmonella* in ground beef and ground pork, respectively. For ground chicken and ground turkey, *Salmonella* was reduced by 1.1 and 0.9 Log CFU/g, respectively.

The effectiveness of the recently approved *Salmonella* lytic phage preparation (SalmoFresh) for the reduction of *Salmonella* in vitro and on chicken breast fillets was examined in combination with lauric arginate (LAE) or cetylpyridinium chloride (CPC) [46]. The combination of phage with CPC or LAE resulted in significant reductions of *Salmonella* between 0.5 and 1.3 Log CFU/g, compared with the control over up to 7 days of refrigerated storage. When the phage was applied sequentially with chemical antimicrobials, all treatments resulted in a significant reduction of *Salmonella*. The application of chlorine (30 ppm) and peracetic acid (400 ppm) followed by phage spray (10^9 PFU/ml) resulted in the highest *Salmonella* reductions of 1.6–1.7 and 2.2–2.5 Log CFU/cm^2, respectively. Wang *et al.* [47] aimed to reduce *Salmonella* and the spoilage bacteria on fresh chilled pork using bacteriophage, nisin, and potassium sorbate (PS), and their combinations. The results showed that all the samples treated with phage significantly reduced the *Salmonella* population on fresh chilled pork. The combination treatment of nisin, PS, and phage (N-PS-P) significantly lowered the total viable counts (TVC), total

volatile base nitrogen, and thiobarbituric acid reactive substances of the chilled pork during the storage period. The TVC of the sample treated by N-PS-P was reduced by 2.3 Log CFU/g after 7 days. Through the electronic nose detection, it was also found that the N-PS-P treatment significantly reduced odor and maintained good sensory qualities of the chilled pork.

Commercially Available Phages and Regulatory Status

Several US federal agencies have issued various degrees of approval for the use of lytic phages for specific and distinct purposes, but hardly any are specific to produce commodities. Even in the USA, the use of phages for biocontrol is considered a relatively new technology and has only recently received regulatory recognition for use in foods. The US Department of Agriculture issued two no objection letters for the use of phages targeting *E. coli* O157:H7 and *Salmonella* spp. developed by Omnilytics, for use as hide sprays on cattle prior to slaughter [26]. A small number of companies, including Micreos, Omnilytics, Novolytics, and Intralytix, obtained FDA-GRAS status for the commercial application of phages to foods [45]. More detailed commercial phage products developed for the use of food and animal products are listed in Table 5. SalmoShield, SalmoLyse, and BioTector are available to control *Salmonella* in foods, pet foods, and animal feed, respectively. It is also promising that the FDA recently approved SalmoFresh – a *Salmonella*-specific cocktail of phages – as GRAS, for direct applications onto poultry, fish, shellfish, and fresh and processed fruits and vegetables [26].

Limitations and Prospects of Phages as Biocontrol Agents

Phages and their hosts persist in a veritable tug-of-war in which bacteria become resistant to their phage and the phage overcomes this resistance [60]. Through various means of cellular modulation, pathogens can become resistant to their phage, especially if the resistant bacteria are allowed to persist in the environment, replicate, and pass the resistance to their daughter cells. Phage resistance can also be acquired in vivo or through gene modifications. However, bacterial resistance can be thwarted by the use of a phage cocktail with multiple phages with multiple surface receptors. This can prevent, or at least delay, bacterial resistance to the phage [59, 61]. This may offer a powerful advantage for the future use of phages to control *Salmonella* spp. in nature and foods that have acquired resistance.

For a broader use of phages in foods, more studies that prove the usefulness and safety of phages from various perspectives should be accumulated and disseminated to the food industry. Current research using phages deals with certain strains of *Salmonella*, such as *Salmonella* Typhimurium and *Salmonella* Enteritidis. As the emerging new *Salmonella* serotypes introduced in this review become more problematic in foods, the complementary phages that can control the specific *Salmonella* serotypes should be developed and characterized. New approaches are required to breed phages

Table 5. Commercial phage products for use of food and animal products.

Product	Application	Description	Company	Country
AgriPhage	Food (tomato)	Targets bacterial spot or bacterial speck on crops against *Xanthomonas campestris* pv. *vesicatoria* or *Pseudomonas syringae* pv. *tomato*	Omnilytics, Inc.	USA
EcoShield	Food	Targets *Escherichia coli* O157:H7 contamination in foods and food processing facilities	Intralytix, Inc.	USA
ListShield	Food	Targets *Listeria monocytogenes* contamination in foods and food processing facilities	Intralytix, Inc.	USA
SalmoShield	Food	Targets selected, highly pathogenic *Salmonella*-serotypes contamination in foods and food processing facilities	Intralytix, Inc.	USA
ShigaShield	Food	Targets *Shigella* spp. contamination in foods and food processing facilities	Intralytix, Inc.	USA
Listex P100	Food	Targets *L. monocytogenes* contamination on food products	Micreos	The Netherlands
Ecolicide	Animal feed	Targets *Escherichia coli* O157:H7 contamination on hides of live animals prior to slaughter	Intralytix, Inc.	USA
SalmoLyse	Animal feed	Targets *Salmonella* contamination in pet food	Intralytix, Inc.	USA
BioTector	Animal feed	Animal feed for control of *Salmonella* in poultry	CheilJedang Co.	Korea
SalmoFresh	Food	Targets *Salmonella enterica* in various foods	Intralytix, Inc.	USA

with extended host ranges for emerging *Salmonella* serotypes and to assemble a cocktail of phages or combine with other hurdle technologies to maximized the efficacy of phage applications. Phages can become an effective component of a hurdle approach and act synergistically when applied with a compatible antimicrobial agent such as bacteriocins [47].

As the advantages of using phages in foods increase, more research should be focused upon the wider aspects of the public acceptance of phages as versatile biocontrol agents. The positive and negative impacts of phages as antimicrobial agents on the quality of foods and food products should be resolved, especially the effects of phages on the sensory, nutritional, or phytochemical properties of the foods to which they are applied. Potential areas of phage applications in the future may include food packaging and food hygiene. Lone *et al*. [62] reported a recent research on the application of phages to food packaging systems as an immobilized packaging material to extend the shelf life of food products. The authors suggested that the cocktails of *E. coli* and *Listeria monocytogenes* phages on cellulose membranes could be used as bioactive antimicrobial packaging materials to enhance the safety of fresh produce and ready-to-eat meat. Another possible phage application may be the use of phages as sanitizers to disinfect the production line, equipment, and environment. In conclusion, phages can play an important role in the enhancement of food safety related to *Salmonella* serotypes in the food industry. The potential efficacy of the phages should be carefully considered, along with various other aspects such as safety and public acceptance as well as long-term effects.

Acknowledgments

This research was supported by the Rural Development Administration (RDA) of Korea, funded by the Cooperative Research Program for Agriculture Science and Technology Development (PJ012290) and the National Research Foundation (NRF) of Korea, funded by Basic Science Research Program (2017R1D1A1B03035195).

Conflict of Interest

The authors have no financial conflicts of interest to declare.

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