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Bacteriophages and its applications: an overview

Sonika Sharma[1] · Soumya Chatterjee[1] · Sibnarayan Datta[1] · Rishika Prasad[1,2] · Dharmendra Dubey[1] · Rajesh Kumar Prasad[1] · Mohan G Vairale[1]

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Abstract Bacteriophages (or phages), the most abundant viral entity of the planet, are omni-present in all the ecosystems. On the basis of their unique characteristics and anti-bacterial property, phages are being freshly evaluated taxonomically. Phages replicate inside the host either by lytic or lysogenic mode after infecting and using the cellular machinery of a bacterium. Since their discovery by Twort and d'Herelle in the early 1900s, phage became an important agent for combating pathogenic bacteria in clinical treatments and its related research gained momentum. However, due to recent emergence of bacterial resistance on antibiotics, applications of phage (phage therapy) become an inevitable option of research. Phage particles become popular as a biotechnological tool and treatment of pathogenic bacteria in a range of applied areas. However, there are few concerns over the application of phage-based solutions. This review deals with the updated phage taxonomy (*ICTV 2015 Release and subsequent revision*) and phage biology and the recent development of its application in the areas of biotechnology, biosensor, therapeutic medicine, food preservation, aquaculture diseases, pollution remediation, and wastewater treatment and issues related with limitations of phage-based remedy.

Sonika Sharma and Soumya Chatterjee contributed equally.

✉ Soumya Chatterjee
drlsoumya@gmail.com

[1] Defence Research Laboratory, DRDO, Tezpur, Assam 784001, India

[2] School of Biomedical Engineering, Cornell University, Ithaca, NY 14850, USA

Introduction

There are billions of viruses on the Earth. An estimation of their number reaches an astronomical figure of about 10^{31} viruses, which is much more than the number of stars in the universe (Weitz and Wilhelm 2013). Most of the viruses play a significant role in the global biogeochemical cycles and thrive by infecting microbes like bacteria, archaea, and microeukaryotes (Suttle 2007). Because of their astounding numbers, and intimate relationship with different microbes, they control both host populations and ecosystem functions (Weitz and Wilhelm 2012). Among the total viral population, bacteriophages, popularly known as phages (Greek "phagein" meaning "to eat"), are the group of viruses that infect and devour bacteria. This potential antibacterial property of phage is unique (Jamalludeen et al. 2009).

Phages are considered to be the most diverse and abundant entity on earth and are thought to exist in every ecosystem (Maranger and Bird 1995; Hendrix 2002; Hanlon 2007; Le Romancer et al. 2007) ranging from extremely hot environments like hot springs, the Sahara, to extremely cold environments like polar inland waters (Breitbart et al. 2004; Glud and Middleboe 2004; Prigent et al. 2005; Suttle 2005; Säwström et al. 2008; Lin et al. 2010). Sea water is among the hugely diverse and most dense natural environments for phages and other viruses; for example, the surface seawater has a concentration of approximately 10 million viruses per milliliter (Breitbart 2012). Similarly, forest floors and agricultural soils usually harbor a phage count of approximately10^8–10^9 per gram of soil (dry mass; Williamson et al. 2003; Williamson et al. 2005). It is also reported that to carry out important ecological functions, phages express a variety of auxiliary metabolic genes (Breitbart 2012; Weitz and Wilhelm 2013).

A single phage particle can hunt for a specific bacterium species or a subset of the same species. After infecting a

bacterium, phages replicate inside it. Once a bacterial cell is infected, phages multiply exponentially using the cellular machinery of the bacteria including protein-synthesizing and energy-generating systems. However, the method of propagation may either be lytic or lysogenic in nature. The lytic phages cause lysis of the host bacterial cells to release progeny viruses (Young et al. 2000). On the other hand, lysogenic or the temperate phages integrate their nucleic acid (genome) within the host bacterial cell and replicate along with the host, conferring new properties to the host bacteria (Brock et al. 1988). Phages are classified on the basis of certain criteria including its host specificity, morphology, nucleic acid type, mode of infection, morphogenesis, phylogeny, serology, sensitivity to physical and chemical agents, and its environment (Abeles et al. 1984). All bacterial genera, including the cyanobacteria, archaebacterial, and mycoplasmas, are known to be vulnerable to a plethora of phages.

Brief history of bacteriophage

British bacteriologist Ernest Hanbury Hankin, in 1896, first reported antibacterial activity in the waters of the river Ganga and the river Yamuna in India (Hankin 1896: http://icmr.nic.in/buapril02.pdf). The then unidentified antibacterial agent was also noted as filterable and heat labile; it was found to limit the spread of cholera epidemic (Hankin 1896; Van Helvoort 1992; Sulakvelidze et al. 2001). However, how the implications of Hankin's findings related to the existence of bacteriophages remain dubious in the scientific society.

In 1915, Frederick William Twort FRS (October 22, 1877–March 20, 1950), an English bacteriologist, superintendent of the Brown Institute for Animals and professor of bacteriology at the University of London, while growing viruses in a laboratory condition, found zones of clearance in the form of "transmissible glassy transformation" with micrococcus bacteria. He also concluded that this agent multiplied itself in the process of killing the bacteria (Twort 1915, 1922, 1949).

On the other hand, Félix d'Herelle (April 25, 1873–February 22, 1949), a French-Canadian microbiologist working at the Pasteur Institute in Paris, observed the bacteriophage phenomenon (in the year 1917) on severe hemorrhagic dysentery among French troops stationed at Maisons-Laffitte. He had observed the same phenomenon in 1910 when he was studying microbiology due to an epizootic locust infection in Mexico. d'Herelle prepared bacteria-free filtrates from fecal samples of patients and incubated the filtrate with the bacterium *Shigella*, isolated from those patients. His primary goal was to develop a vaccine against bacterial dysentery. For observing the growth of the bacteria, an aliquot of the filtrate-bacteria mixture was spread on agar medium and incubated. d'Herelle found the appearance of small, clear zones, which he primarily termed *taches*, then *taches vierges*, and later, *plaques*. This finding was presented in September 1917 and subsequently published (d'Herelle 1917, 1930; Summers 1999; Sulakvelidze et al. 2001). d'Herelle also proposed that the phenomenon was caused by a bacteria parasitizing virus and named "bacteriophage"—*phages* implying to "eat" or "devour" bacteria. As per the recollection of d'Herelle, the name "bacteriophage" was decided together with his wife Marie, and the word came into existence on 18 October 1916—the day before their youngest daughter's birthday (d'Herelle 1930; Summers 1999; Sulakvelidze et al. 2001). Thus, the credit of discovery of bacteriophages goes independently to two scientists: F.W. Twort and Félix d'Herelle. Primarily, the scientific society first called it "Twort-d'Herelle phenomenon," and later, the "bacteriophage phenomenon" (d'Herelle 1949; Duckworth 1976; Sulakvelidze et al. 2001).

Structure of bacteriophage

Length of phages varies widely and usually ranges from 24 to 200 nm (Mayer 2016). T4 phages are among the largest phages that are approximately 200 nm in length and 80–100 nm wide. Phages having an icosahedral shape or a shape with 20 sides and filaments are also common (http://www.microrao.com/micronotes/bacteriophage.pdf). After the first commercial production of transmission electron microscope (called "Hypermicroscope") by Siemens and Halske Company (Germany) in 1939, photomicrography of bacteriophages came into the existence. Ruska (1940) and Pfankuch and Kausche (1940), both working in the same company, reported separately in the same journal and on same date showing the first pictures of bacteriophages to the scientific world (Ruska 1940; Pfankuch and Kausche 1940; Ackermann, 2011a, b). On the other hand, in North America, Prebus and Hillier of University of Toronto constructed separately the first electron microscope in 1938, and subsequently, commercialized the same after years of research by Hiller at Radio Corporation of America (RCA, Princeton, NJ; Prebus and Hillier 1939; Haguenau et al. 2003; Ackermann 2011a, b). Luria and Anderson, in 1942, reported different unstained coli and staphylococcal phage particles, which were renamed later as T2 (T-even type; Luria and Anderson 1942; Ackermann 2011a, b). Despite continental difference, huge political unrest (because of World War II) and extreme limitations on scientific exchange, interestingly, both the group of scientists were aware of other progress in the development of this extremely important scientific instrument (Pfankuch and Kausche 1940; Ackermann 2011a, b). Later on, using the "negative contrast" technique in an electron microscope, Brenner and his team first reported a clearer image of bacteriophages in 1959 (Brenner and Horne 1959; Brenner et al. 1959). In subsequent years, Bradley and Kay (1960) and Bradley (1967) elaborated fine structures of phages. The basic features of a typical bacteriophage, in this case the T4 bacteriophage, include a "head" or capsid and a "tail" (Fig. 1).

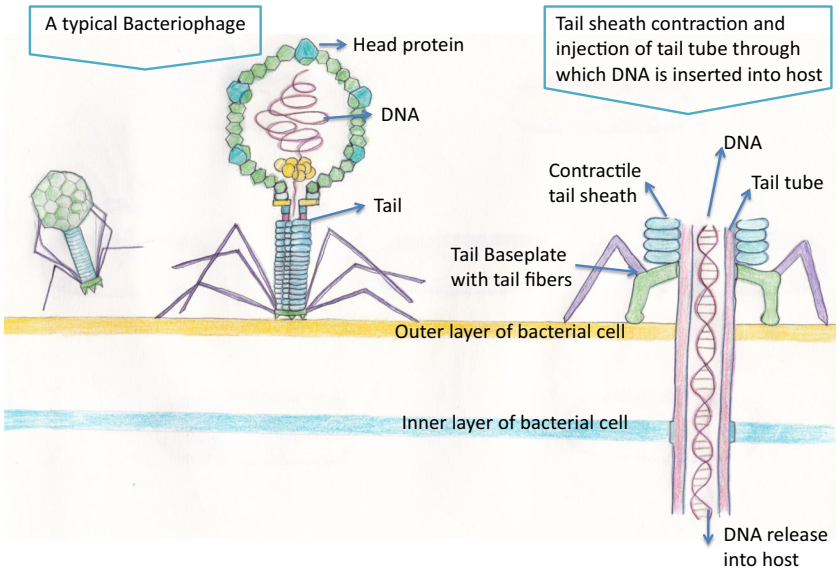

Fig. 1 Schematic representation of a typical structure of a phage emphasizing tail region and contractile ability to insert its DNA into host bacterial cell by penetrating cell wall

The head or capsid structure, regardless of its size or shape, is a congregation of one or more protein subunits called protomers. The morphological subunit of a capsid is a capsomere which protects the viral nucleic acid (genome). The tail is a hollow tube through which the nucleic acid passes when the bacteriophage infects a bacterial host cell. Some phages do not possess a tail. The T4 phage has additional structures, namely the base plate and tail fibers attached to the tail that aid the phage in attaching itself to a bacterial cell (Leiman et al. 2003).

Taxonomy of phages

As mentioned earlier, there are billions and billions of phages. Deciphering taxonomic characterization is a challenging task, especially for such nano-sized phage particles. In 1967, phages were first classified by Bradley and were subsequently approved by the International Committee on Taxonomy of Viruses (ICTV) and total 111 phages were listed in classification (Wildy 1971). Bradley's classification projected six basic morphological types of tailed phages that further, categorized on the basis of morphotypes (contractile tails, long and noncontractile tails, and short tails), small isometric ssDNA viruses, filamentous phages, and small ssRNA phages. The regulating body for the viral taxonomic system (ICTV) characterizes phage particles taking into consideration numerous parameters like host range, physical characteristics (such as structure, capsid size, and shape), type of genomic material (single or double-stranded DNA or RNA), genome size, and resistance to organic solvents (Murphy et al. 1995). More than 96 % of phages are tailed and carries dsDNA as genetic material; however, they may vary in shape like cubic, filamentous, and pleomorphic (Ackermann 2011a, b). Polyphasic taxonomy was revised and emphasis was given on genomic relationship (Thompson et al. 2015). Earlier in 2008, only 18 genera and 36 species were listed among three caudoviral families, Myoviridae, Podoviridae, and Siphoviridae. Subsequently, the order caudovirales expanded and an updated and detailed bacteriophage classification was presented in ICTV Release 2015 (http://www.ictvonline.org/virusTaxonomy.asp; Krupovic et al. 2016). Some alterations have also been suggested by committee, like replacement of word "phage" with "virus" in prokaryotic virus taxon names, omission of infix "like" from prokaryotic virus genus names, discouragement of use of "Phi" and other Greek letters in prokaryotic virus genera, exclusion of hyphens, and encouragement to use of host genus name in replacement of taxon names is being encouraged to avoid confusion related to phage action on specific bacterial host (Krupovic et al. 2016; Pietilä et al. 2016). The overview of the various bacteriophage families has been included in Table 1 compiled from (ICTV 2015 Release; EC 47, London, UK, July 2015 Email ratification 2016 (MSL #30) for ready reference to the readers.

Mechanism of proliferation

Specific receptors (like lipopolysaccharides, teichoic acids, proteins, and flagella) on the surface of the host bacteria are required for the phage to infect the bacteria. Due to this specificity of the receptor present on the bacterial cell surface, phages can infect specific hosts only. However, in solution, this interaction with the host is a random phenomenon for the phages. Bacterial type (Gram-negative and Gram-positive), growth conditions, and virulence also influence the phage to attach on the host's surface (Rakhuba et al. 2010). The outer membrane of Gram-negative bacteria has an external lipopolysaccharide (LPS) layer and embedded outer membrane

Table 1 The overview of the various phage families compiled from International Committee on Taxonomy of Viruses (ICTV 2015 Release; http://www.ictvonline.org/virusTaxonomy.asp)

Order	Family	Subfamily	Genus	Host bacteria	Species	Accession number (example species)	Isolate (example species)
Caudovirales (linear, dsDNA)	*Myoviridae* (Icosahedral head with contractile tail)	*Eucampyvirinae*	*Cp220virus*	*Campylobacter*	*Campylobacter virus CP21*	HE815464	
					Campylobacter virus CP220	FN667788	
					Campylobacter virus CPt10	FN667789	
					Campylobacter virus IBB35	HM246720	
			Cp8virus		*Campylobacter virus CP81*	FR823450	
					Campylobacter virus CPX	JN132397	
					Campylobacter virus NCTC12673	GU296433	
		Peduovirinae	*Hp1virus*	*Aeromonas*	*Aeromonas virus phiO18P*		
				Haemophilus	*Haemophilus virus HP1*		
					Haemophilus virus HP2		
				Pasteurella	*Pasteurella virus F108*		
				Vibrio	*Vibrio virus K139*		
					Vibrio virus Kappa		
			P2virus	*Burkholderia*	*Burkholderia virus phi52237*		
					Burkholderia virus phiE122		
					Burkholderia virus phiE202		
				Escherichia	*Escherichia virus 186*		
					Escherichia virus P2		
					Escherichia virus Wphi		
				Mannheimia	*Mannheimia virus MhaA1-PHL101*		
				Pseudomonas	*Pseudomonas virus phiCTX*		
				Ralstonia	*Ralstonia virus RSA1*		
				Salmonella	*Salmonella virus Fels2*		
					Salmonella virus PsP3		
					Salmonella virus SopEphi		
				Yersinia	*Yersinia virus L413C*		
		Spounavirinae	*Kayvirus*	*Staphylococcus*	*Staphylococcus virus G1*		
					Staphylococcus virus G15	JQ686190	Staphylococcus phage G15
					Staphylococcus virus JD7	JX878671	Staphylococcus phage JD007
					Staphylococcus virus K		
					Staphylococcus virus MCE2014	KJ888149	Staphylococcus phage MCE-2014
					Staphylococcus virus P108	KM216423	Staphylococcus phage P108
					Staphylococcus virus S253	AB853330	Staphylococcus phage S25-3
					Staphylococcus virus SA12	AB903967	Staphylococcus phage phiSA12
			P100virus	*Listeria*	*Listeria virus A511*		
					Listeria virus P100	DQ004855	Listeria phage P100
			Silviavirus	*Staphylococcus*	*Staphylococcus virus Remus*	JX846613	Staphylococcus phage vB_SauM_Remus
					Staphylococcus virus SA11	JX194239	Staphylococcus phage SA11
			Spo1virus	*Bacillus*	*Bacillus virus SPO1*		

Table 1 (continued)

Order	Family	Subfamily	Genus	Host bacteria	Species	Accession number (example species)	Isolate (example species)
			Twortvirus	*Staphylococcus*	*Staphylococcus virus Twort*		
			Unassigned	*Enterococcus*	*Enterococcus virus phiEC24C*		
				Lactobacillus	*Lactobacillus phage Lb338-1*	FJ822135	
					Lactobacillus virus LP65		
		Tevenvirinae	*Cc31virus*	*Enterobacter*	*Enterobacter virus CC31*	GU323318	Enterobacter phage CC31
					Enterobacter virus PG7	KJ101592	Enterobacter phage PG7
			Js98virus	*Escherichia*	*Escherichia virus Bp7*	HQ829472	Escherichia phage Bp7
					Escherichia virus IME08	HM071924	Escherichia phage IME08
					Escherichia virus JS10	EU863409	Escherichia phage JS10
					Escherichia virus JS98		
					Escherichia virus VR5	KP007359	Escherichia phage vb_EcoM-VR5
			Rb49virus		*Escherichia virus phi1*		
					Escherichia virus RB49		
			Rb69virus		*Escherichia virus HX01*	JX536493	Escherichia phage HX01
					Escherichia virus JS09	KF582788	Escherichia phage vB_EcoM_JS09
					Escherichia virus RB69		
				Shigella	*Shigella virus UTAM*	KM407600	Shigella phage Shf125875
			S16virus	*Salmonella*	*Salmonella virus S16*	HQ331142	Salmonella phage vB_SenM-S16
					Salmonella virus STML198	JX181825	Salmonella phage STML-198
			Schizot4virus	*Vibrio*	*Vibrio virus KVP40*		
					Vibrio virus nt1		
					Vibrio virus ValKK3	KP671755	Vibrio phage ValKK3
			Sp18virus	*Escherichia*	*Escherichia virus VR7*	HM563683	Escherichia phage vB_EcoM_VR7
					Escherichia virus VR20	KP007360	Escherichia phage vB_EcoM_VR20
					Escherichia virus VR25	KP007361	Escherichia phage vB_EcoM_VR25
					Escherichia virus VR26	KP007362	Escherichia phage vB_EcoM_VR26
				Shigella	*Shigella virus SP18*	GQ981382	Shigella phage SP18
			T4virus	*Escherichia*	*Escherichia virus AR1*	AP011113	Escherichia phage AR1
					Escherichia virus C40	JN986846	Escherichia phage vB_EcoM_ACG-C40
					Escherichia virus E112	KJ668714.2	Escherichia phage vB_EcoM_112
					Escherichia virus ECML134	JX128259	Escherichia phage ECML-134
					Escherichia virus Ime09	JN202312	Escherichia phage ime09
					Escherichia virus RB3	KM606994	Escherichia phage RB3
					Escherichia virus RB14		

Table 1 (continued)

Order	Family	Subfamily	Genus	Host bacteria	Species	Accession number (example species)	Isolate (example species)
					Escherichia virus T4		
				Shigella	*Shigella virus Pss1*	KM501444	Shigella phage pSs-1
					Shigella virus Shfl2	HM035025	Shigella phage Shfl2
				Yersinia	*Yersinia virus D1*	HE956711	Yersinia phage phiD1
					Yersinia virus PST	KF208315	Yersinia phage PST
			Unassigned	*Acinetobacter*	*Acinetobacter virus 133*		
				Aeromonas	*Aeromonas virus 65*		
					Aeromonas virus Aeh1		
				Enterobacteria	*Enterobacteria virus SV14*		
				Escherichia	*Escherichia virus RB16*		
					Escherichia virus RB32		
					Escherichia virus RB43		
				Pseudomonas virus 42	*Pseudomonas virus 42*		
		Vequintavirinae	*Cr3virus*	*Cronobacter*	*Cronobacter virus CR3*	JQ691612	Cronobacter phage CR3
					Cronobacter virus CR8	KC954774	Cronobacter phage CR8
					Cronobacter virus CR9	JQ691611	Cronobacter phage CR9
					Cronobacter virus GAP31	JN882284	Cronobacter phage vB_CsaM_GAP31
				Escherichia	*Escherichia virus 4MG*	KF550303	Escherichia phage 4MG
				Salmonella	*Salmonella virus SE1*	GU070616	Salmonella phage SE1
					Salmonella virus SSE121	JX181824	Salmonella phage SSE121
			Se1virus	*Escherichia*	*Escherichia virus FFH2*	KJ190158	Escherichia phage FFH2
					Escherichia virus FV3	JQ031132	Escherichia phage FV3
					Escherichia virus JES2013	KC690136	Escherichia phage JES2013
					Escherichia virus V5	DQ832317	Escherichia phage V5
			Agatevirus	*Bacillus*	*Bacillus virus Agate*	JX238501	Bacillus phage phiAGATE
					Bacillus virus Bobb	KM051843	Bacillus phage Bobb
					Bacillus virus Bp8pC	KJ010547	Bacillus phage Bp8p–C
			Ap22virus	*Acinetobacter*	*Acinetobacter virus AB1*	HM368260	Acinetobacter phage AB1
					Acinetobacter virus AB2	JX976549	Acinetobacter phage vB_AbaM-IME-AB2
					Acinetobacter virus AbC62	KJ817802	Acinetobacter phage YMC-13-01-C62
					Acinetobacter virus AP22	HE806280	Acinetobacter phage AP22
			B4virus	*Bacillus*	*Bacillus virus B4*	JN790865	Bacillus phage B4
					Bacillus virus Bigbertha	KF669647	Bacillus phage BigBertha
					Bacillus virus Riley	KJ489402	Bacillus phage Riley
					Bacillus virus Spock	KF669662	Bacillus phage Spock
					Bacillus virus Troll	KF208639	Bacillus phage Troll
			Bastillevirus		*Bacillus virus Bastille*	JF966203	Bacillus phage Bastille
					Bacillus virus CAM003	KJ489397	Bacillus phage CAM003
			Bc431virus		*Bacillus virus Bc431*	JX094431.1	Bacillus phage vB_BceM_Bc431v3
					Bacillus virus Bcp1	KJ451625.1	Bacillus phage Bcp1

Table 1 (continued)

Order	Family	Subfamily	Genus	Host bacteria	Species	Accession number (example species)	Isolate (example species)
					Bacillus virus BCP82	KJ081346.1	Bacillus phage BCP8–2
					Bacillus virus JBP901	KJ676859.1	Bacillus phage JBP901
			Bcep78virus	*Burkholderia*	*Burkholderia virus Bcep1*		
					Burkholderia virus Bcep43		
					Burkholderia virus Bcep781		
					Burkholderia virus BcepNY3		
				Xanthomonas	*Xanthomonas virus OP2*		
			Bcepmuvirus	*Burkholderia*	*Burkholderia virus BcepMu*		
					Burkholderia virus phiE255		
			Biquartavirus	*Aeromonas*	*Aeromonas virus 44RR2*	AY375531	Aeromonas phage 44RR2.8t
			Bxz1virus	*Mycobacterium*	*Mycobacterium virus I3*		
			Cd119virus	*Clostridium*	*Clostridium virus phiC2*		
					Clostridium virus phiCD27		
					Clostridium virus phiCD119		
			Cp51virus	*Bacillus*	*Bacillus virus CP51*	KF554508.2	Bacillus phage CP-51
					Bacillus virus JL	KC595512.2	Bacillus phage JL
					Bacillus virus Shanette	KC595513.2	Bacillus phage Shanette
			Cvm10virus	*Escherichia*	*Escherichia virus CVM10*	GU903191	Escherichia phage vB_EcoM_ECO1230-10
					Escherichia virus ep3	KM360178	Escherichia phage vB_EcoM-ep3
			Felixo1virus	*Erwinia*	*Erwinia virus Ea214*		
				Escherichia	*Escherichia virus AYO145A*	KR014248	Escherichia phage vB_EcoM_AYO145A
					Escherichia virus EC6	JX560968	Escherichia phage EC6
					Escherichia virus JH2	KF055347	Escherichia phage JH2
					Escherichia virus VpaE1	KM657822	Escherichia phage vB_EcoM-VpaE1
					Escherichia virus wV8		
				Salmonella	*Salmonella virus FelixO1*		
					Salmonella virus HB2014	KP010413	Salmonella phage HB-2014
					Salmonella virus Mushroom	KP143762	Salmonella phage Mushroom
					Salmonella virus UAB87	JN225449	Enterobacteriaphage UAB_Phi87
			Hapunavirus	*Halomonas virus HAP1*	*Halomonas virus HAP1*		
				Vibrio virus VP882	*Vibrio virus VP882*		
			Kpp10virus	*Pseudomonas*	*Pseudomonas virus Ab03*	LN610573	Pseudomonas phage vB_PaeM_PAO1_Ab03
					Pseudomonas virus KPP10	AB472900.2	Pseudomonas phage KPP10
					Pseudomonas virus PAKP3	KC862299	Pseudomonas phage PAK_P3
			Muvirus	*Escherichia*	*Escherichia virus Mu*		
			Myohalovirus	*Halobacterium*	*Halobacterium virus phiH*		
			Nit1virus	*Bacillus*	*Bacillus virus Grass*	KF669652	Bacillus phage Grass
					Bacillus virus NIT1	AP013029	Bacillus phage phiNIT1

Table 1 (continued)

Order	Family	Subfamily	Genus	Host bacteria	Species	Accession number (example species)	Isolate (example species)
					Bacillus virus SPG24	AB930182	Bacillus phage SPG24
			P1virus	*Aeromonas*	*Aeromonas virus 43*		
				Escherichia	*Escherichia virus P1*		
			Pakpunavirus	*Pseudomonas*	*Pseudomonas virus CAb1*	HE983845	Pseudomonas phage vB_PaeM_C2-10_Ab1
					Pseudomonas virus CAb02	LN610572	Pseudomonas phage vB_PaeM_C2-10_Ab02
					Pseudomonas virus JG004	GU988610.2	Pseudomonas phage JG004
					Pseudomonas virus PAKP1	KC862297	Pseudomonas phage PAK_P1
					Pseudomonas virus PAKP4	KC862300	Pseudomonas phage PAK_P4
					Pseudomonas virus PaP1	HQ832595	Pseudomonas phage PaP1
			Pbunavirus	*Burkholderia*	*Burkholderia virus BcepF1*		
				Pseudomonas	*Pseudomonas virus 141*		
					Pseudomonas virus Ab28	LN610589	Pseudomonas phage vB_PaeM_C1–14_Ab28
					Pseudomonas virus DL60	KR054030	Pseudomonas phage DL60
					Pseudomonas virus DL68	KR054033	Pseudomonas phage DL68
					Pseudomonas virus F8		
					Pseudomonas virus JG024	GU815091	Pseudomonas phage JG024
					Pseudomonas virus KPP12	AB560486	Pseudomonas phage KPP12
					Pseudomonas virus LBL3		
					Pseudomonas virus LMA2		
					Pseudomonas virus PB1		
					Pseudomonas virus SN		
			Phikzvirus		*Pseudomonas virus EL*		
					Pseudomonas virus Lin68		
					Pseudomonas virus phiKZ		
			Rheph4virus	*Rhizobium*	*Rhizobium virus RHEph4*	JX483876	Rhizobium phage RHEph04
			Secunda5virus	*Aeromonas*	*Aeromonas virus 25*	DQ529280	Aeromonas phage 25
					Aeromonas virus 31		
					Aeromonas virus Aes12	JN377895	Aeromonas phage Aes012
					Aeromonas virus Aes508	JN377894	Aeromonas phage Aes508
					Aeromonas virus AS4	HM452125	Aeromonas phage phiAS4
				Stenotrophomonas	*Stenotrophomonas virus IME13*	JX306041	Stenotrophomonas phage IME13
			Tg1virus	*Yersinia*	*Yersinia virus R1RT*	HE956709	Yersinia phage phiR1-RT
					Yersinia virus TG1	KP202158	Yersinia phage vB_YenM_TG1
			Unassigned	*Bacillus*	*Bacillus virus G*		
					Bacillus virus PBS1		
				Microcystis	*Microcystis virus Ma-LMM01*		
			VhmLvirus	*Vibrio virus*	*Vibrio virus MAR*	JX556417	Vibrio phage vB_VpaM_MAR
					Vibrio virus VHML	AY133112	Vibrio phage VHML
					Vibrio virus VP585	FN297812	Vibrio phage VP585
			Vi1virus	*Dickeya*	*Dickeya virus Limestone*		

Table 1 (continued)

Order	Family	Subfamily	Genus	Host bacteria	Species	Accession number (example species)	Isolate (example species)
				Escherichia virus	*Escherichia virus CBA120*		
					Escherichia virus ECML4	JX128257	Escherichia phage ECML-4
					Escherichia virus PhaxI		
				Salmonella	*Salmonella virus Det7*	KP797973	Salmonella phage Det7
					Salmonella virus Marshall	KF669653	Salmonella phage Marshall
					Salmonella virus Maynard	KF669654	Salmonella phage Maynard
					Salmonella virus SFP10		
					Salmonella virus SH19		
					Salmonella virus SJ2	KJ174317	Salmonella phage vB_SalM_SJ2
					Salmonella virus SJ3	KJ174318	Salmonella phage vB_SalM_SJ3
					Salmonella virus STML131	JX181828	Salmonella phage STML-13-1
					Salmonella virus ViI		
				Shigella	*Shigella virus AG3*		
			Wphvirus	*Bacillus*	*Bacillus virus WPh*	HM144387	Bacillus phage W.Ph.
	Podoviridae (Icosahedral head with short tail)	*Autographivirinae*	*Kp34virus*	*Klebsiella*	*Klebsiella virus F19*	KF765493.2	Klebsiella phage F19
					Klebsiella virus K244	AB716666	Klebsiella phage NTUH-K2044-K1–1
					Klebsiella virus KP34	GQ413938.2	Klebsiella phage KP34
					Klebsiella virus SU503	KP708985	Klebsiella phage vB_KpnP_SU503
					Klebsiella virus SU552A	KP708986	Klebsiella phage vB_KpnP_SU552A
			Phikmvvirus	*Pantoea*	*Pantoea virus Limelight*		
					Pantoea virus Limezero		
				Pseudomonas	*Pseudomonas virus LKA1*		
					Pseudomonas virus phiKMV		
			Sp6virus	*Erwinia virus Era103*	*Erwinia virus Era103*		
				Escherichia	*Escherichia virus K5*		
					Escherichia virus K1-5		
					Escherichia virus K1E		
				Salmonella	*Salmonella virus SP6*		
			T7virus	*Escherichia*	*Escherichia virus T7*		
				Kluyvera	*Kluyvera virus Kvp1*		
				Pseudomonas	*Pseudomonas virus gh1*		
			Unassigned	*Prochlorococcus*	*Prochlorococcus virus PSSP7*		
				Synechococcus	*Synechococcus virus P60*		
					Synechococcus virus Syn5		
		Picovirinae	*P68virus*	*Staphylococcus*	*Staphylococcus virus 44AHJD*		
					Streptococcus virus C1		
			Phi29virus	*Bacillus*	*Bacillus virus B103*		

Table 1 (continued)

Order	Family	Subfamily	Genus	Host bacteria	Species	Accession number (example species)	Isolate (example species)
					Bacillus virus GA1		
					Bacillus virus phi29		
				Kurthia	*Kurthia virus 6*		
			Unassigned	*Actinomyces*	*Actinomyces virus Av1*		
				Mycoplasma	*Mycoplasma virus P1*		
				Streptococcus	*Streptococcus virus Cp1*		
			Bcep22likevirus	*Burkholderia*	*Burkholderia virus Bcep22*	AY349011	
					Burkholderia virus Bcepil02	FJ937737	
					Burkholderia virus Bcepmigl	JX104231	
					Burkholderia virus DC1	JN662425	
			Bpp1virus	*Bordetella*	*Bordetella virus BPP1*		
				Burkholderia	*Burkholderia virus BcepC6B*		
			Cba41virus	*Cellulophaga*	*Cellulophaga virus Cba41*	KC821632	Cellulophaga phage phi4:1
					Cellulophaga virus Cba172	KC821609	Cellulophaga phage phi17:2
			Epsilon15virus	*Escherichia*	*Escherichia virus phiV10*		
				Salmonella	*Salmonella virus Epsilon15*		
			F116virus	*Pseudomonas*	*Pseudomonas virus F116*	AY625898	
					Pseudomonas virus H66	KC262634	
			G7cvirus	*Escherichia*	*Escherichia virus APEC5*	KF192075	Escherichia phage vB_EcoP_PhAPEC5
					Escherichia virus APEC7	KF562340	Escherichia phage vB_EcoP_PhAPEC7
					Escherichia virus Bp4	KJ135004.2	Escherichia phage Bp4
					Escherichia virus EC1UPM	KC206276.2	Escherichia phage EC1-UPM
					Escherichia virus ECBP1	JX415535	Escherichia phage ECBP1
					Escherichia virus G7C	HQ259105	Escherichia phage vB_EcoP_G7C
					Escherichia virus IME11	JX880034	Escherichia phage IME11
				Shigella	*Shigella virus Sb1*	KF620435	Shigella phage pSb-1
			Lit1virus	*Pseudomonas*	*Pseudomonas virus Ab09*	HG962375	Pseudomonas phage vB_PaeP_C2-10_Ab09
					Pseudomonas virus LIT1	FN422399	Pseudomonas phage LIT1
					Pseudomonas virus PA26	JX194238	Pseudomonas phage PA26
			Luz24virus	*Pseudomonas*	*Pseudomonas virus Ab22*	LN610578	Pseudomonas phage vB_PaeP_C2-10_Ab22
					Pseudomonas virus CHU	KP233880	Pseudomonas phage PhiCHU
					Pseudomonas virus LUZ24		
					Pseudomonas virus PAA2	KF856712	Pseudomonas phage phiIBB-PAA2
					Pseudomonas virus PaP3		
					Pseudomonas virus PaP4	KC294142	Pseudomonas phage PaP4
					Pseudomonas virus TL	HG518155	Pseudomonas phage TL
			N4virus	*Escherichia*	*Escherichia virus N4*		

Table 1 (continued)

Order	Family	Subfamily	Genus	Host bacteria	Species	Accession number (example species)	Isolate (example species)
			Nonanavirus	*Salmonella*	*Salmonella virus 9NA*	KJ802832	Salmonella phage 9NA
					Salmonella virus SP069	KC139649	Salmonella phage SP069
			P22virus	*Salmonella*	*Salmonella virus HK620*		
					Salmonella virus P22		
					Salmonella virus ST64T		
				Shigella	*Shigella virus Sf6*		
			Pagevirus	*Bacillus*	*Bacillus virus Page*	KF669655	Bacillus phage Page
					Bacillus virus Palmer	KP411017	Bacillus phage Palmer
					Bacillus virus Pascal	KM236247	Bacillus phage Pascal
					Bacillus virus Pony	KF669660	Bacillus phage Pony
					Bacillus virus Pookie	KM236248	Bacillus phage Pookie
			Phieco32virus	*Escherichia*	*Escherichia virus ECB2*	JX415536	Escherichia phage ECBP2
					Escherichia virus NJ01	JX867715	Escherichia phage NJ01
					Escherichia virus phiEco32		
					Escherichia virus Septima11	KF981730	Escherichia phage KBNP1711
					Escherichia virus SU10	KM044272	Escherichia phage vB_EcoP_SU10
			Unassigned	*Hamiltonella*	*Hamiltonella virus APSE1*		
				Lactococcus	*Lactococcus virus KSY1*		
				Phormidium	*Phormidium virus WMP3*		
					Phormidium virus WMP4		
				Pseudomonas	*Pseudomonas virus 119X*		
				Roseobacter	*Roseobacter virus SIO1*		
				Vibrio	*Vibrio virus VpV262*		
			Vp5virus	*Vibrio*	*Vibrio virus VC8*	JF712866	Vibrio phage phiVC8
					Vibrio virus VP2	AY505112	Vibriophage VP2
					Vibrio virus VP5	AY510084	Vibriophage VP5
	Siphoviridae (Icosahedral head with Long and noncontractile Tail)	*Guernseyvirinae*	*Jerseyvirus*	*Salmonella*	*Salmonella phage L13*	KC832325	Salmonella phage L13
					Salmonella phage LSPA1	KM272358	Salmonella phage LSPA1
					Salmonella virus AG11	JX297445	Salmonella phage vB_SenS_AG11
					Salmonella virus Ent1	HE775250	
					Salmonella virus Jersey	KF148055	
					Salmonella virus SE2	JQ007353	
					Salmonella virus SETP3	EF177456	
					Salmonella virus SETP7	KF562865	Salmonella phage SETP7
					Salmonella virus SETP13	KF562864	Salmonella phage SETP13
					Salmonella virus SP101	KC139511	Salmonella phage FSL SP-101
					Salmonella virus SS3e	AY730274	
					Salmonella virus wksl3	JX202565	
			K1gvirus	*Escherichia*	*Escherichia virus K1G*	GU196277	Escherichia phage K1G
					Escherichia virus K1H	GU196278	Escherichia phage K1H
					Escherichia virus K1ind1	GU196279	Escherichia phage K1ind1
					Escherichia virus K1ind2	GU196280	Escherichia phage K1ind2
			Sp31virus	*Salmonella*	*Salmonella virus SP31*	KC139518	Salmonella phage FSL SP-031

Table 1 (continued)

Order	Family	Subfamily	Genus	Host bacteria	Species	Accession number (example species)	Isolate (example species)
		Tunavirinae	*Kp36virus*	*Enterobacter*	*Enterobacter virus F20*		
				Klebsiella	*Klebsiella virus 1513*	KP658157	Klebsiella phage 1513
					Klebsiella virus KP36	JF501022	Klebsiella phage KP36
			Rogue1virus	*Escherichia*	*Escherichia virus AHP42*	KF771237	Escherichia phage vB_EcoS_AHP42
					Escherichia virus AHS24	KF771238	Escherichia phage vB_EcoS_AHS24
					Escherichia virus AKS96	KF771239	Escherichia phage vB_EcoS_AKS96
					Escherichia virus E41c	KJ668713	Escherichia phage e4/1c
					Escherichia virus Eb49		
					Escherichia virus Jk06		
					Escherichia virus KP26	KC579452	Escherichia phage phiKP26
					Escherichia virus Rogue1	KC333879	Escherichia phage Rogue1
			Rtpvirus	*Escherichia*	*Escherichia virus ACGM12*	JN986845	Escherichia phage vB_Eco_ACG-M12
					Escherichia virus Rtp	AM156909	Escherichia phage Rtp
			T1virus	*Escherichia*	*Escherichia virus ADB2*	JX912252	Escherichia phage ADB-2
					Escherichia virus T1		
				Shigella \	*Shigella virus PSf2*	KP085586	Shigella phage pSf-2
					Shigella virus Shfl1		
			Tlsvirus	*Citrobacter*	*Citrobacter virus Stevie*	KM236241	Citrobacter phage Stevie
				Escherichia	*Escherichia virus TLS*	AY308796	Escherichia phage Tls
				Salmonella	*Salmonella virus SP126*	KC139513	Salmonella phage FSL SP-126
			Unassigned	*Cronobacter*	*Cronobacter virus Esp2949-1*		
			Andromedavirus	*Bacillus*	*Bacillus virus Andromeda*	KC330684	
					Bacillus virus Blastoid	KF669648	
					Bacillus virus Curly	KC330679	
					Bacillus virus Eoghan	KC330680	
					Bacillus virus Finn	KC330683	
					Bacillus virus Glittering	KF669651	
					Bacillus virus Riggi	KF669659	
					Bacillus virus Taylor	KC330682	
			Barnyardvirus	*Mycobacterium*	*Mycobacterium virus Barnyard*	AY129339	
					Mycobacterium virus Konstantine	FJ174691	
					Mycobacterium virus Patience	JN412589	
					Mycobacterium virus Predator	EU770222	
			Bignuzvirus	*Mycobacterium*	*Mycobacterium virus Bignuz*	JN412591	
					Mycobacterium virus Jebeks	JN572061	
			Biseptimavirus	*Staphylococcus*	*Staphylococcus virus 13*	AF424783	

Table 1 (continued)

Order	Family	Subfamily	Genus	Host bacteria	Species	Accession number (example species)	Isolate (example species)
					Staphylococcus virus 77	AY508486	
					Staphylococcus virus 108PVL	AB243556	
			Bronvirus	*Mycobacterium*	*Mycobacterium virus Bron*	HM152763	
					Mycobacterium virus Faith1	JF744988	
					Mycobacterium virus Joedirt	JF704108	
					Mycobacterium virus Rumpelstiltskin	JN680858	
			C2virus	*Lactococcus*	*Lactococcus virus bIL67*		
					Lactococcus virus c2		
			C5virus	*Lactobacillus*	*Lactobacillus virus c5*	EU340421	
					Lactobacillus virus LLKu	AY739900	
			Cba181virus	*Cellulophaga*	*Cellulophaga virus Cba121*	KC821613	Cellulophaga phage phi12:1
					Cellulophaga virus Cba171	KC821617	Cellulophaga phage phi17:1
					Cellulophaga virus Cba181	KC821619	Cellulophaga phage phi18:1
			Cbastvirus	*Cellulophaga*	*Cellulophaga virus ST*	HQ634192	Cellulophaga phage phiST
			Cecivirus	*Bacillus*	*Bacillus virus 250*	GU229986	
					Bacillus virus IEBH	EU874396	
			Charlievirus	*Mycobacterium*	*Mycobacterium virus Charlie*	JN256079	
					Mycobacterium virus Redi	JN624851	
			Che8virus	*Mycobacterium*	*Mycobacterium virus Ardmore*	GU060500	
					Mycobacterium virus Avani	JQ809702	
					Mycobacterium virus Boomer	EU816590	
					Mycobacterium virus Che8	AY129330	
					Mycobacterium virus Che9d	AY129336	
					Mycobacterium virus Deadp	JN698996	
					Mycobacterium virus Dlane	JF937093	
					Mycobacterium virus Dorothy	JX411620	
					Mycobacterium virus Dotproduct	JN859129	
					Mycobacterium virus Drago	JN542517	
					Mycobacterium virus Fruitloop	FJ174690	
					Mycobacterium virus Gumbie	JN398368	
					Mycobacterium virus Ibhubesi	JF937098	
					Mycobacterium virus Llij	DQ398045	
					Mycobacterium virus Mozy	JF937102	
					Mycobacterium virus Mutaforma13	JN020142	

Table 1 (continued)

Order	Family	Subfamily	Genus	Host bacteria	Species	Accession number (example species)	Isolate (example species)
					Mycobacterium virus Pacc40	FJ174692	
					Mycobacterium virus PMC	DQ398050	
					Mycobacterium virus Ramsey	FJ174693	
					Mycobacterium virus Rockyhorror	JF704117	
					Mycobacterium virus SG4	JN699012	
					Mycobacterium virus Shauna1	JN020141	
					Mycobacterium virus Shilan	JN020143	
					Mycobacterium virus Spartacus	JQ300538	
					Mycobacterium virus Taj	JX121091	
					Mycobacterium virus Tweety	EF536069	
					Mycobacterium virus Wee	HQ728524	
					Mycobacterium virus Yoshi	JF704115	
			Che9cvirus	*Mycobacterium*	*Mycobacterium virus Babsiella*	JN699001	
					Mycobacterium virus Brujita	FJ168659	
					Mycobacterium virus Che9c	AY129333	
			Chivirus	*Salmonella*	*Salmonella virus Chi*	JX094499	
					Salmonella virus FSLSP030	KC139519	
					Salmonella virus FSLSP088	KC139512	
					Salmonella virus iEPS5	KC677662	
					Salmonella virus SPN19	JN871591	
			Cjw1virus	*Mycobacterium*	*Mycobacterium virus 244*	DQ398041	
					Mycobacterium virus Bask21	JF937091	
					Mycobacterium virus CJW1	AY129331	
					Mycobacterium virus Eureka	JN412590	
					Mycobacterium virus Kostya	EU816591	
					Mycobacterium virus Porky	EU816588	
					Mycobacterium virus Pumpkin	GQ303265	
					Mycobacterium virus Sirduracell	JF937106	
					Mycobacterium virus Toto	JN006061	
			Corndogvirus	*Mycobacterium*	*Mycobacterium virus Corndog*	AY129335	
					Mycobacterium virus Firecracker	JN698993	
			D3112virus	*Pseudomonas*	*Pseudomonas virus D3112*	AY394005	
					Pseudomonas virus DMS3	DQ631426	

Table 1 (continued)

Order	Family	Subfamily	Genus	Host bacteria	Species	Accession number (example species)	Isolate (example species)
					Pseudomonas virus FHA0480	JN808773	
					Pseudomonas virus LPB1	HE584812	
					Pseudomonas virus MP22	DQ873690	
					Pseudomonas virus MP29	EU272036	
					Pseudomonas virus MP38	EU272037	
					Pseudomonas virus PA1KOR	HM624080	
			D3virus	*Pseudomonas*	*Pseudomonas virus D3*	AF165214	
					Pseudomonas virus PMG1	HQ711985	
			E125virus	*Burkholderia*	*Burkholderia virus phi6442*	CP000625	
					Burkholderia virus phi1026b	AY453853	
					Burkholderia virus phiE125	AF447491	
			Ff47virus	*Mycobacterium*	*Mycobacterium virus Ff47*	JX901189	Mycobacterium virus FF47
					Mycobacterium virus Muddy	KF024728	Mycobacterium virus Muddy
			Hk578virus	*Escherichia*	*Escherichia virus HK578*	JQ086375	
					Escherichia virus JL1	JX865427	
					Escherichia virus SSL2009a	FJ750948	
				Shigella	*Shigella virus EP23*	JN984867	
				Sodalis	*Sodalis virus SO1*	GQ502199	
			L5virus	*Mycobacterium*	*Mycobacterium virus Alma*	JN699005	
					Mycobacterium virus Arturo	JX307702	
					Mycobacterium virus Astro	JX015524	
					Mycobacterium virus Backyardigan	JF704093	
					Mycobacterium virus BBPiebs31	JF957057	
					Mycobacterium virus Benedict	JN083852	
					Mycobacterium virus Bethlehem	AY500153	
					Mycobacterium virus Billknuckles	JN699000	
					Mycobacterium virus Bruns	JN698998	
					Mycobacterium virus Bxb1	AF271693	
					Mycobacterium virus Bxz2	AY129332	
					Mycobacterium virus Che12	DQ398043	
					Mycobacterium virus Cuco	JN408459	
					Mycobacterium virus D29		
					Mycobacterium virus Doom	JN153085	
					Mycobacterium virus Ericb	JN049605	
					Mycobacterium virus Euphoria	JN153086	
						JF704107	

Table 1 (continued)

Order	Family	Subfamily	Genus	Host bacteria	Species	Accession number (example species)	Isolate (example species)
					Mycobacterium virus George		
					Mycobacterium virus Gladiator	JF704097	
					Mycobacterium virus Goose	JX307704	
					Mycobacterium virus Hammer	JF937094	
					Mycobacterium virus Heldan	JF957058	
					Mycobacterium virus Jasper	EU744251	
					Mycobacterium virus JC27	JF937099	
					Mycobacterium virus Jeffabunny	JN699019	
					Mycobacterium virus JHC117	JF704098	
					Mycobacterium virus KBG	EU744248	
					Mycobacterium virus Kssjeb	JF937110	
					Mycobacterium virus Kugel	JN699016	
					Mycobacterium virus L5		
					Mycobacterium virus Lesedi	JF937100	
					Mycobacterium virus LHTSCC	JN699015	
					Mycobacterium virus lockley	EU744249	
					Mycobacterium virus Marcell	JX307705	
					Mycobacterium virus Microwolf	JF704101	
					Mycobacterium virus Mrgordo	JN020140	
					Mycobacterium virus Museum	JF937103	
					Mycobacterium virus Nepal	JQ698665	
					Mycobacterium virus Packman	JF704110	
					Mycobacterium virus Peaches	GQ303263	
					Mycobacterium virus Perseus	JN572689	
					Mycobacterium virus Pukovnik	EU744250	
					Mycobacterium virus Rebeuca	JX411619	
					Mycobacterium virus Redrock	GU339467	
						JN398369	

Table 1 (continued)

Order	Family	Subfamily	Genus	Host bacteria	Species	Accession number (example species)	Isolate (example species)
					Mycobacterium virus Ridgecb		
					Mycobacterium virus Rockstar	JF704111	
					Mycobacterium virus Saintus	JN831654	
					Mycobacterium virus Skipole	GU247132	
					Mycobacterium virus Solon	EU826470	
					Mycobacterium virus Switzer	JF937108	
					Mycobacterium virus SWU1	JF946695	
					Mycobacterium virus Ta17a	JN400277	
					Mycobacterium virus Tiger	JQ684677	
					Mycobacterium virus Timshel	JF957060	
					Mycobacterium virus Trixie	JN408461	
					Mycobacterium virus Turbido	JN408460	
					Mycobacterium virus Twister	JQ512844	
					Mycobacterium virus U2	AY500152	
					Mycobacterium virus Violet	JN687951	
					Mycobacterium virus Wonder	HM755814	
				Rhodococcus	*Rhodococcus virus RER2*	JN116827	
					Rhodococcus virus RGL3	JN116826	
			Lambdavirus	*Escherichia*	*Escherichia virus HK022*		
					Escherichia virus HK97		
					Escherichia virus Lambda		
			Liefievirus	*Mycobacterium*	*Mycobacterium virus Halo*	DQ398042	
					Mycobacterium virus Liefie	JN412593	
			N15virus	*Escherichia*	*Escherichia virus N15*		
			Nonagvirus	*Escherichia*	*Escherichia virus 9 g*	KJ419279	Enterobacteria phage 9 g
					Escherichia virus JenK1	KP719134	Enterobacteria phage JenK1
					Escherichia virus JenP1	KP719132	Enterobacteria phage JenP1
					Escherichia virus JenP2	KP719133	Enterobacteria phage JenP2
			Omegavirus	*Mycobacterium*	*Mycobacterium virus Baka*	JF937090	
					Mycobacterium virus Courthouse	JN698997	
					Mycobacterium virus Littlee	JF937101	
					Mycobacterium virus Omega	AY129338	
					Mycobacterium virus Optimus	JF957059	

Table 1 (continued)

Order	Family	Subfamily	Genus	Host bacteria	Species	Accession number (example species)	Isolate (example species)
					Mycobacterium virus Thibault	JN201525	
			P23virus	*Thermus*	*Thermus virus P23–45*	EU100883	
					Thermus virus P74–26	EU100884	
			P70virus	*Listeria*	*Listeria virus LP26*	KJ094020	Listeria phage LP-026
					Listeria virus LP37	JX126920.2	Listeria phage LP-037
					Listeria virus LP110	JX126919	Listeria phage LP-110
					Listeria virus LP114	KJ094021	Listeria phage LP-114
					Listeria virus P70	JX442241	Listeria phage P70
			Pbi1virus	*Mycobacterium*	*Mycobacterium virus PBI1*	DQ398047	
					Mycobacterium virus Acadian	JN699007	
					Mycobacterium virus Athena	JN699003	
					Mycobacterium virus Chrisnmich	JF704094	
					Mycobacterium virus Cooper	DQ398044	
					Mycobacterium virus Gadjet	JN698992	
					Mycobacterium virus Nigel	EU770221	
					Mycobacterium virus Oline	JN192463	
					Mycobacterium virus Pg1	AF547430	
					Mycobacterium virus Pipefish	DQ398049	
					Mycobacterium virus Rosebush	AY129334	
					Mycobacterium virus Stinger	JN699011	
					Mycobacterium virus Zemanar	JF704104	
			Phic31virus	*Streptomyces*	*Streptomyces virus phiBT1*	AJ550940	
					Streptomyces virus phiC31		
					Streptomyces virus TG1	JX182372	
			Phicbkvirus	*Caulobacter*	*Caulobacter virus Karma*	JX100811	
					Caulobacter virus Magneto	JX100812	
					Caulobacter virus phiCbK	JX100813	
					Caulobacter virus Rogue	JX100814	
					Caulobacter virus Swift	JX100809	
			Phietavirus	*Staphylococcus*	*Staphylococcus virus 11*	AF424781	
					Staphylococcus virus 29	AY954964	
					Staphylococcus virus 37	AY954958	
					Staphylococcus virus 53	AY954952	
					Staphylococcus virus 55	AY954963	
					Staphylococcus virus 69	AY954951	
					Staphylococcus virus 71	AY954962	

Table 1 (continued)

Order	Family	Subfamily	Genus	Host bacteria	Species	Accession number (example species)	Isolate (example species)
					Staphylococcus virus 80	DQ908929	
					Staphylococcus virus 85	AY954953	
					Staphylococcus virus 88	AY954966	
					Staphylococcus virus 92	AY954967	
					Staphylococcus virus 96	AY954960	
					Staphylococcus virus 187	AY954950	
					Staphylococcus virus 52a	AY954965	
					Staphylococcus virus 80alpha	DQ517338	
					Staphylococcus virus CNPH82	DQ831957	
					Staphylococcus virus EW	AY954959	
					Staphylococcus virus IPLA5	JN192400	
					Staphylococcus virus IPLA7	JN192401	
					Staphylococcus virus IPLA88	EU861004	
					Staphylococcus virus PH15	DQ834250	
					Staphylococcus virus phiETA	AP001553	
					Staphylococcus virus phiETA2	AP008953	
					Staphylococcus virus phiETA3	AP008954	
					Staphylococcus virus phiMR11	AB370268	
					Staphylococcus virus phiMR25	AB370205	
					Staphylococcus virus phiNM1	DQ530359	
					Staphylococcus virus phiNM2	DQ530360	
					Staphylococcus virus phiNM4	DQ530362	
					Staphylococcus virus SAP26	GU477322	
					Staphylococcus virus X2	AY954968	
			Phifelvirus	*Enterococcus*	*Enterococcus virus FL1*	GQ478081	
					Enterococcus virus FL2	GQ478084	
					Enterococcus virus FL3	GQ478086	
			Phijl1virus	*Lactobacillus*	*Lactobacillus virus ATCC8014*	JX486087	
					Lactobacillus virus phiJL1	AY236756	
				Pediococcus	*Pediococcus virus cIP1*	JN051154	
			Psavirus	*Listeria*	*Listeria virus LP302*	JX120799.2	Listeria phage LP-030-2
					Listeria virus PSA	AJ312240.2	Listeria phage PSA
			Psimunavirus	*Methanobacterium*			

Table 1 (continued)

Order	Family	Subfamily	Genus	Host bacteria	Species	Accession number (example species)	Isolate (example species)
					Methanobacterium virus psiM1		
			Reyvirus	*Mycobacterium*	*Mycobacterium virus Bongo*	JN699628	
					Mycobacterium virus Rey	JF937105	
			Sap6virus	*Enterococcus*	*Enterococcus virus BC611*	AB712291	
					Enterococcus virus IMEEF1	KF192053	
					Enterococcus virus SAP6	JF731128	
					Enterococcus virus VD13	KJ094032	
				Streptococcus	*Streptococcus virus SPQS1*	HE962497	
			Septima3virus	*Burkholderia*	*Burkholderia virus KL1*	JF939047	Burkholderia phage vB_BceS_KL1
				Pseudomonas	*Pseudomonas virus 73*	NC_007806	Pseudomonas phage 73
					Pseudomonas virus Ab26	HG962376	Pseudomonas phage vB_PaeS_SCH_Ab26
					Pseudomonas virus Kakheti25	JQ307387	Pseudomonas phage vB_Pae-Kakheti25
			Seuratvirus	*Escherichia*	*Escherichia virus Cajan*	KP064094	Escherichia phage CAjan
					Escherichia virus Seurat	KM236243	Escherichia phage Seurat
			Sextaecvirus	*Staphylococcus*	*Staphylococcus virus SEP9*	KF929199	Staphylococcus phage vB_SepS_SEP9
					Staphylococcus virus Sextaec	KJ804259	Staphylococcus phage 6ec
			Sfi11virus	*Streptococcus*	*Streptococcus virus 858*	EF529515	
					Streptococcus virus 2972	AY699705	
					Streptococcus virus ALQ132	FJ226752	
					Streptococcus virus O1205	U88974	
					Streptococcus virus Sfi11	AF158600	
			Sfi21dt1virus	*Streptococcus*	*Streptococcus virus 7201*	AF145054	
					Streptococcus virus DT1	AF085222	
					Streptococcus virus phiAbc2	FJ236310	
					Streptococcus virus Sfi19	AF115102	
					Streptococcus virus Sfi21	AF115103	
			Sitaravirus	*Paenibacillus*	*Paenibacillus virus Diva*	KP296791	Paenibacillus phage Diva
					Paenibacillus virus Hb10c2	KP202972	Paenibacillus phage HB10c2
					Paenibacillus virus Rani	KP296793	Paenibacillus phage Rani
					Paenibacillus virus Shelly	KP296795	Paenibacillus phage Shelly
					Paenibacillus virus Sitara	KP296796	Paenibacillus phage Sitara
			Sk1virus	*Lactococcus*	*Lactococcus virus 712*	DQ227763	
					Lactococcus virus ASCC191	JQ740813	
					Lactococcus virus ASCC273	JQ740788	
					Lactococcus virus ASCC281	JQ740787	
					Lactococcus virus ASCC465	JQ740804	
					Lactococcus virus ASCC532	JQ740789	
					Lactococcus virus Bibb29	EU221285	
					Lactococcus virus bIL170	AF009630	

Table 1 (continued)

Order	Family	Subfamily	Genus	Host bacteria	Species	Accession number (example species)	Isolate (example species)
					Lactococcus virus CB13	FJ848882	
					Lactococcus virus CB14	FJ848883	
					Lactococcus virus CB19	FJ848884	
					Lactococcus virus CB20	FJ848885	
					Lactococcus virus jj50	DQ227764	
					Lactococcus virus P2	GQ979703	
					Lactococcus virus P008	DQ054536	
					Lactococcus virus sk1	AF011378	
					Lactococcus virus Sl4	FJ848881	
			Slashvirus	*Bacillus*	*Bacillus virus Slash*	KF669661	Bacillus phage Slash
					Bacillus virus Stahl	KP696447	Bacillus phage Stahl
					Bacillus virus Staley	KF669663	Bacillus phage Staley
					Bacillus virus Stills	KP696448	Bacillus phage Stills
			Spbetavirus	*Bacillus*	*Bacillus virus SPbeta*		
			Ssp2virus	*Vibrio*	*Vibrio virus MAR10*	JX556418	Vibrio phage vB_VpaS_MAR10
					Vibrio virus SSP002	JQ692107	Vibrio phage SSP002
			T5virus	*Escherichia*	*Escherichia virus AKFV33*		
					Escherichia virus BF23		
					Escherichia virus DT57C	KM979354	Escherichia phage DT57C
					Escherichia virus EPS7		
					Escherichia virus FFH1	KJ190157	Escherichia phage vB_EcoS_FFH_1
					Escherichia virus H8		
					Escherichia virus T5		
				Salmonella	*Salmonella virus Shivani*	KP143763	Salmonella phage Shivani
					Salmonella virus SPC35		
					Salmonella virus Stitch	KM236244	Salmonella phage Stitch
			Tm4virus	*Mycobacterium*	*Mycobacterium virus Anaya*	JF704106	
					Mycobacterium virus Angelica	HM152764	
					Mycobacterium virus Crimd	HM152767	
					Mycobacterium virus Fionn	JN831653	
					Mycobacterium virus Jaws	JN185608	
					Mycobacterium virus Larva	JN243855	
					Mycobacterium virus Macncheese	JX042579	
					Mycobacterium virus Pixie	JF937104	
					Mycobacterium virus TM4	AF068845	
			Tp21virus	*Bacillus*	*Bacillus virus BMBtp2*	JX887877	
					Bacillus virus TP21	EU887664	
			Triavirus	*Staphylococcus*	*Staphylococcus virus 47*	AY954957	
					Staphylococcus virus 3a	AY954956	
					Staphylococcus virus 42e	AY954955 EU861005	

Table 1 (continued)

Order	Family	Subfamily	Genus	Host bacteria	Species	Accession number (example species)	Isolate (example species)
					Staphylococcus virus IPLA35		
					Staphylococcus virus phi12	AF424782	
					Staphylococcus virus phiSLT	AB045978	
			Wbetavirus	*Bacillus*	*Bacillus virus Wbeta*	DQ289555	
			Xp10virus	*Xanthomonas*	*Xanthomonas virus CP1*	AB720063	
					Xanthomonas virus OP1	AP008979	
					Xanthomonas virus phi17	EU717894	
					Xanthomonas virus Xop411	DQ777876	
					Xanthomonas virus Xp10	AY299121	
			Yuavirus	*Alphaproteobacteria*	*Alphaproteobacteria virus phiJl001*		
				Pseudomonas	*Pseudomonas virus M6*		
					Pseudomonas virus Yua		
Unassigned	*Corticoviridae* (Circular dsDNA, Lipid present in capsid)		*Corticovirus*	*Pseudoalteromonas*	*Pseudoalteromonas virus PM2*		
	Cystoviridae (dsRNA, icosahedral. Enveloped)		*Cystovirus*	*Pseudomonas*	*Pseudomonas virus phi6*		
	Inoviridae (Circular ssDNA, Filamentous)		*Inovirus*	*Escherichia*	*Escherichia virus AE2*		
					Escherichia virus DeltaA		
					Escherichia virus Ec9		
					Escherichia virus f1		
					Escherichia virus fd		
					Escherichia virus HR		
					Escherichia virus I22		
					Escherichia virus If1		
					Escherichia virus M13		
					Escherichia virus PR64FS		
					Escherichia virus SF		
					Escherichia virus tf1		
					Escherichia virus X		
					Escherichia virus X2		
					Escherichia virus ZJ2		
				Pseudomonas	*Pseudomonas virus Pf1*		
					Pseudomonas virus Pf2		
					Pseudomonas virus Pf3		
				Salmonella	*Salmonella virus C2*		
					Salmonella virus IKe		
				Vibrio	*Vibrio virus 493*		
					Vibrio virus CTXphi		
					Vibrio virus fs1		
					Vibrio virus fs2		
					Vibrio virus v6		

Table 1 (continued)

Order	Family	Subfamily	Genus	Host bacteria	Species	Accession number (example species)	Isolate (example species)
					Vibrio virus Vf12		
					Vibrio virus Vf33		
					Vibrio virus VSK		
				Xanthomonas	*Xanthomonas irus Cf16*		
					Xanthomonas virus Cf1c		
					Xanthomonas virus Cf1t		
					Xanthomonas virus Cf1tv		
					Xanthomonas virus Lf		
					Xanthomonas virus Xf		
					Xanthomonas virus Xfo		
					Xanthomonas virus Xfv		
			Plectrovirus	*Acholeplasma*	*Acholeplasma virus MV-L51*		
				Spiroplasma	*Spiroplasma virus 1aa*		
					Spiroplasma virus C74		
					Spiroplasma virus KC3		
					Spiroplasma virus R8A2B		
					Spiroplasma virus S102		
					Spiroplasma virus T78		
	Leviviridae (ssRNA+, icosahedral)		*Allolevivirus*	*Escherichia*	*Escherichia virus FI*		
					Escherichia virus Qbeta		
			Levivirus		*Escherichia virus BZ13*		
					Escherichia virus MS2		
	Microviridae (ssDNA, icosahedral)	*Bullavirinae*	*Alpha3microvirus*	*Escherichia*	*Escherichia virus alpha3*		
					Escherichia virus ID21	DQ079870	Escherichia phage ID21
					Escherichia virus ID32	DQ079871	Escherichia phage ID32
					Escherichia virus ID62	DQ079876	Escherichia phage ID62
					Escherichia virus NC28	DQ079875	Escherichia phage NC28
					Escherichia virus NC29	DQ079879	Escherichia phage NC29
					Escherichia virus NC35	DQ079872	Escherichia phage NC35
					Escherichia virus phiK		
					Escherichia virus St1		
					Escherichia virus WA45	DQ079874	Escherichia phage WA45
			G4microvirus	*virus G4*	*Escherichia virus G4*		
					Escherichia virus ID52	DQ079877	Escherichia phage ID52
					Escherichia virus Talmos	DQ079869	Escherichia phage ID2 Moscow/ID/2001
			Phix174microvirus	*Escherichia*	*Escherichia virus phiX174*		
		Gokushovirinae	*Bdellomicrovirus*	*Bdellovibrio*	*Bdellovibrio virus MAC1*		
					Bdellovibrio virus MH2K		
			Chlamydiamicrovirus	*Chlamydia*	*Chlamydia virus Chp1*		
					Chlamydia virus Chp2		
					Chlamydia virus CPAR39		
					Chlamydia virus CPG1		
			Spiromicrovirus	*Spiroplasma*	*Spiroplasma virus SpV4*		
			Plasmavirus	*Acholeplasma*	*Acholeplasma virus L2*		

Table 1 (continued)

Order	Family	Subfamily	Genus	Host bacteria	Species	Accession number (example species)	Isolate (example species)
	Plasmaviridae (Circular dsDNA, Lipid Envelop *dsDNA*)						
	Pleolipoviridae (Pleomorphic membrane vesicle enclosing single and double stranded DNA genomes)		*Alphapleolipovirus*	*Haloarcula*	*Haloarcula virus HHPV-1*	GU321093	Haloarcula hispanica pleomorphic virus 1
					Haloarcula virus HHPV-2	KF056323	Haloarcula hispanica pleomorphic virus 2
					Halorubrum virus HRPV-1	FJ685651	Halorubrum pleomorphic virus 1
					Halorubrum virus HRPV-2	JN882264	Halorubrum pleomorphic virus 2
					Halorubrum virus HRPV-6	JN882266	Halorubrum pleomorphic virus 6
			Betapleolipovirus	*Halogeometricum*	*Halogeometricum virus HGPV-1*	JN882267	Halogeometricum pleomorphic virus 1
				Halorubrum	*Halorubrum virus HRPV-3*	JN882265	Halorubrum pleomorphic virus 3
			Gammapleolipovirus	*Haloarcula*	*Haloarcula virus His2*	AF191797	His2 virus
	Sphaerolipoviridae (Icosahedral. tailless haloarchaeal)		*Alphasphaerolipovirus*	*Haloarcula*	*Haloarcula hispanica icosahedral virus 2*	JN968479	
					Haloarcula hispanica virus PH1	KC252997	
					Haloarcula hispanica virus SH1	AY950802	
			Betasphaerolipovirus	*Natrinema*	*Natrinema virus SNJ1*	AY048850	
			Gammasphaerolipovirus	*Thermus*	*Thermus virus IN93*	AB063393	
					Thermus virus P23-77	GQ403789	
	Tectiviridae (Icosahedral Non-Enveloped Linear dsDNA)		*Tectivirus*	*Bacillus*	*Bacillus virus AP50*		
					Bacillus virus Bam35		
				Salmonella	*Salmonella virus PRD1*		
				Thermus	*Thermus virus P37-14*		
			Unassigned	*Alicyclobacillus*	*Alicyclobacillus virus NS11*		

proteins (OMPs) for transport and diffusion of nutrients. These act as phage receptors, and in some infection strategies, they are essential for adsorption of phage particles as well (Bugla-Ploskonska et al. 2007; Rakhuba et al. 2010). In comparison, teichoic acids (peptidoglycan interspersed with acid polysaccharides) present in the Gram-positive bacteria cell wall act as receptors for their corresponding phages (Brown et al. 2013; León and Bastías 2015).

The penetration processes in bacterial cell also vary in different phage groups. In general, myoviridae phage inserts its genetic material into the bacterial cell by using a syringe-like movement of its tail (Fig. 2). After receptor recognition, in a reversible binding mode, the phage particle attaches its base plate with the bacterial surface utilizing the flexing activity of tail fibers. The phage takes sufficient time to make its surface binding irreversible. Thereafter, with the help of ATP, the contraction of its tail takes place, along with insertion of its genetic material. On the contrary, podoviridae phage, which is devoid of the tail part of the myoviridae phage, inserts its genetic material after enzymatically degrading a portion of the bacterial cell membrane using its small, tooth-like tail fibers (Rakhuba et al. 2010; Brown et al. 2013; León and Bastías 2015).

Phages undergo two possible life cycles: lytic and lysogenic cycles.

Lytic cycle

Phages, which are in their lytic phase, are called virulent phages. During the lytic cycle, lysis (death) of host bacterium occurs as the phage multiplies in great numbers within the host, following which the phage disintegrates and ruptures the host cell for release of new phage particles (Fig. 2).

The lytic cycle initiates with the attachment of the phage on the bacteria with the aid of a complex of proteins (Karlsson et al. 2003). Once the attachment of the viral particle is complete, the genetic material of the bacteriophage is inserted into the bacterial host cell. Upon penetration, the bacterial metabolic machinery is utilized by the phage to create multiple copies of its own genetic material (DNA or RNA). DNA viruses directly transcribe themselves into mRNA (messenger RNA) molecules that are then used to direct the host cell's ribosomes. In case of RNA viruses (retroviruses), a unique enzyme—reverse transcriptase—transcribes the viral RNA into DNA, and thereafter, follows the path of DNA virus for transcription of the viral RNA. Towards the later stages of this translation, the newly translated proteins are assembled to form the capsid and the tail of the phages that break out of the host cell, bursting its cellular membrane. Each newly formed particle continues to infect new host cells and subsequently proliferates. In few cases, instead of the phage genome, host chromosome gets packed in to the capsid during phage replication and represents an example of horizontal gene transfer within the bacterial population via transduction (Madigan and Martinko 2006). A direct application of phages exhibiting only the lytic cycle is that they can be conveniently employed for tackling the problem of antibiotic-resistant pathogenic bacteria.

Lysogenic cycle

In comparison to the lytic cycle, the lysogenic phase is exhibited particularly by temperate phages (Campbell and Reece 2005), and results in the integration of the viral genetic material with the bacterial genome (called prophage), ensuring continued replication of the viral genetic

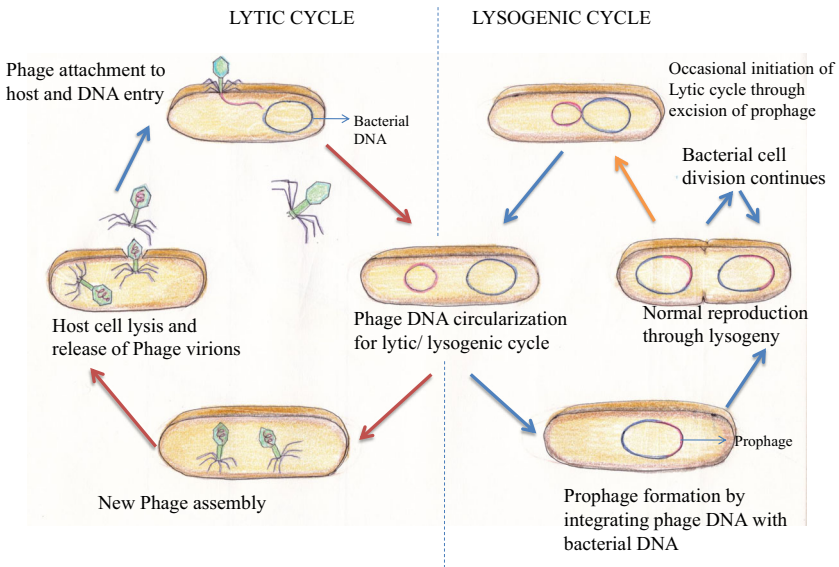

Fig. 2 Schematic representation of lytic and lysogenic cycle of phage

material without any fatal consequences to the infected host (Inal 2003). However, due to incorporation of viral genetic material into the host, change in the phenotype of the infected bacteria is a common phenomenon. This conversion may induce the pathogenicity of bacteria, which is evident for many common bacterial strains (Brussow et al. 2004; Keen 2012). Prevention of such lysogenic conversion may also be done using hydrogen peroxide by production of a reactive oxygen species, glutathione, and overexpression of transcriptional repressors (Wagner et al. 2001; Liu et al. 2005; Ptashne 2006; Keen 2012).

Application of phages

Biotechnological relevance

Recently, phages have become an important instrument to biotechnologists. It is being studied for various purposes like drug designing, synthesis of novel protein, delivery of protein and DNA vaccines, detection of pathogenic bacteria, and screening of protein libraries, peptides, or antibodies (Hart et al. 1994; Sperinde et al. 2001; Clark and March 2004; Donnelly et al. 2015; Gao et al. 2015). Further, phages are being used as a substitute to antibiotics for many antibiotic-resistant bacterial strains, biocontrol agents in agriculture, aquaculture, and oil and petroleum industry (Haq et al. 2012). Researchers are also working upon synthesizing a novel peptide by exploiting phage display techniques, gene inclusion, and replication using host machinery (Smith 1985; Sidhu 2000; Haq et al. 2012; Wang et al. 2016). Phage display was first described by Smith (1985) to identify polypeptides with precise bait-binding activity; the technique has evolved with several versatile applications (Paschke 2006; Li and Caberoy 2010). The displayed molecule encoded by the phage genetic information will be expressed on its surface along with the coat protein. Researchers reported using phages like M13, Lambda, and T7 for phage display techniques (Benhar 2001; Willats 2002; Wang et al. 2016). A range of ligands can be prepared by fusing the coat protein gene with different gene-encoding peptides. Such ligands must have capabilities like detecting viable bacteria like *Escherichia coli* (Wang et al. 2016) and targeting specific pathogen proteins, recognizing specific receptors, and blocking interaction between ligand and receptor (Watson and Eveland 1965; Kodikara et al. 1991; Funatsu et al. 2002; Haq et al. 2012). Furthermore, bacteriophages are being modified as tunable nano-containers for the packaging and delivering of peptides (Kelly et al. 2015). In an interesting study, Dickerson et al. (2005) demonstrated the use of engineered filamentous bacteriophage in cocaine sequestration for blocking the behavioral effects of cocaine in rodent model. Furthermore, phage technology for detecting affinity of antibody to a particular antigen (pathogenic) or phage amplification for detecting pathogenic bacteria, like *Mycobacterium tuberculosis*, *E. coli*, *Pseudomonas*, etc., improvised research in this field (Stewart et al. 1989; Barry et al. 1996; Donnelly et al. 2015). Exploring phage sensitivity and specificity to design phage-based biosensors can be an improved alternative to antibody-based immunoassay techniques (Peltomaa et al. 2015).

Medicine and clinical application

About a century ago, in 1917, the bacteriophage era was started when Félix d'Herelle published a paper demonstrating "un bactériophage obligatoire" (d'Herelle 1917, 1949; Abedon et al. 2011). Bruynoghe and Maisin (1921) initiated bacteriophage therapy by treating patients having staphylococcal infections. "Phage therapy" has become a potential therapeutic option (Duckworth and Gulig 2002; Wright et al. 2009a, b; Sarker et al. 2012). Immense research has been initiated to employ phage therapy as an alternative (Matsuzaki et al. 2003; Quintin et al. 2005; Chatterjee et al. 2015; Cui 2015; Zschach et al. 2015; Abedon 2016; Maszewska et al. 2016). Phage based products were first developed in the commercial laboratory of d'Herelle in Paris. Treatment of various pathogens and antibiotic-resistance bacteria (like *Salmonella* spp. *Clostridium difficile*, and diarrheagenic *E. coli*) has been tried using phage (Mai et al. 2010; Frampton et al. 2012). Phage-based products were first developed in the commercial laboratory of d'Herelle in Paris. The company (later became the successful French company L'Oréal) produced five phage preparations (Bacté-coli-phage, Bacté-rhinophage, Bacté-intesti-phage, Bacté-pyo-phage, and Bacté-staphyphage) (Summers 1999; Sulakvelidze et al. 2001). In 1940s, Eli Lilly and Company (Indianapolis, IN, USA) developed seven phage products for human uses. These products were either in the form of a lysate in broth cultures (e.g., Colo-lysate, Ento-lysate, Neiso-lysate, and Staphylo-lysate) or in the form of a water soluble jelly (e.g., Colo-jel, Ento-jel, and Staphylo-jel) against targeted bacteria like, staphylococci, streptococci, and *Escherichia coli*. They were used for treating abscesses, septic wounds and vaginitis, mastoid infections, and respiratory tract infections (Sulakvelidze et al. 2001).

However, due to exponential growth of antibiotic-based drug companies and pharmaceutical giant companies, phage products became less popular (Alisky et al. 1998; Sulakvelidze and Kutter 2005). In favor of therapeutic uses of phages, recent reports on the application of phage cocktails for open septic wounds and burn injuries have contributed encouraging results. Phage cocktail containing 82 phages against *Pseudomonas aeruginosa* and 8 phages against *Staphylococcus aureus* was successfully applied on eight patients (Merabishvili et al. 2009; Wright et al., 2009a, b; Nilsson 2014). Recently, Pherecydes Pharma, a biotechnology company in France, have announced the phase I/II single-blind multicenter clinical trials of its

bacteriophage based product 'Phagoburn' (http://www.pherecydes-pharma.com/phagoburn-clinical-study.html; Reardon 2014; Ravat et al. 2015; Servick 2016). Phagoburn contains bacteriophage cocktail targeting pathogenic strain of *Escherichia coli* and *Pseudomonas aeruginosa* and its infection in serious burn patients. The Phagoburn is a collaborative European project (www.phagoburn.eu) coordinated by French Ministry of Defense and being conducted in eleven major burns units in France, Switzerland and Belgium along with eight civilian hospitals. Phage therapy is important alternative to overcome critical limitations of antibiotic therapy due to emergence of bacterial resistance, like, in the case of *Clostridium difficile* infection (CDI). CDI is responsible for inducing the dysbiosis, which has extremely high recurrence rates. As per reports, treatment of CDI using current antibiotics has become more and more ineffective (Sangster et al. 2014). Further, prolonged use of antibiotics can also harm beneficial gut flora causing discomfort to the patients. Phage therapy against *C. difficile* involves specifically targeting the causative agent, sparing the other bacterial organisms of the human gut (Sangster et al. 2014, 2015). Similarly, treatment of nosocomial infections (common hospital-acquired infections) caused by *Pseudomonas aeruginosa* is a huge therapeutic challenge currently. High rate of morbidity and mortality is connected with the infection, along with a greater possibility of drug resistance in the bacteria during the course of therapy. With such limited scope for developing new drugs, scientists have also found considerable success in alternative treatment options including phage-based approaches (Viertel et al. 2014; Chatterjee et al. 2015). Babalova et al. (1968) used *Shigella* phages to treat bacterial dysentery and successfully controlled dysentery in patients. Till date, inadequate references are available on human clinical trials conducted and published; the reported cases are phase I studies and mostly from European Medicines Agency (EMA) or United States Food and Drug Administration (FDA) jurisdictions (Bruttin and Brüssow 2005; Merabishvili et al. 2009; Rhoads et al. 2009). In 2009, phase I clinical trial of bacteriophage cocktail (Biophage-PA) targeting three pathogenic strains of *S. aureus*, *P. aeruginosa*, and *E. coli* targeting venous ulcers was approved US FDA (Rhoads et al. 2009). Similarly, a randomized, double-blind, placebo-controlled phase I/II clinical trial approved by UK Medicines and Healthcare products Regulatory Agency (MHRA) and the Central Office for Research Ethics Committees (COREC) ethical review process was performed to treat chronic otitis against multidrug resistant bacteria *P. aeruginosa* and found lower bacterial count and significant improvement with a single input dose of 600,000 bacteriophages (Wright et al. 2009a, b). Bacteriophage application trials have shown that PFU count of 10^2–10^3 plaque forming unit (PFU) is adequate to counter 10^6–10^9 CFU per milliliter proliferation threshold of bacteria in vivo (Marza et al. 2006; Wright et al. 2009a, b; Parracho et al. 2012). However, the reported trials with bacteriophages have been performed with 10^5 and 10^9 PFU of individual bacteriophages (Bruttin and Brüssow 2005; Merabishvili et al. 2009; Rhoads et al. 2009; Wright et al. 2009a, b). Development of *phage bioderm* is another important area of application in clinical sector. It is a therapeutic autodegrading, non-toxic, biopolymer complex containing phages that help in healing of wounds and burns, osteomyelitis, and periodontal diseases (Mathur et al. 2003). Studies reported 20–95 % lysis of clinical isolates of *Serratia marcescens* using specific phage strains and phage type (Alisky et al. 1998). However, there are certain limitations on the application of phage bioderm, like reduction in phage activity due to development of antibodies against phages, induction of toxin genes, and fast discharge of bacterial endotoxins due to the lytic effect of phage (Mathur et al. 2003).

Biosensor development

IUPAC defines a biosensor as "a device that uses specific biochemical reactions mediated by isolated enzymes, immune-systems, tissues, organelles or whole cells to detect chemical compounds usually by electrical, thermal or optical signals" (Nagel et al. 1992; Hwang 2014). A biosensor is typically composed of bio-based recognition and transducer components, and electronic systems (signal amplification, processing, and display). Potential applications of biosensors are diverse and numerous, from defense security to pharmaceutical science to environmental monitoring and assessment (Kirsch et al. 2013). Biosensors have a number of advantages like sensitivity, specificity, speed and accuracy of detection, easy sample preparation, cost-effectiveness, etc. (Singh et al. 2013; Hwang 2014; Rackus et al. 2015). Like that of many other biomaterials, unique biological, geometrical, and mechanical characters of bacteriophages can be exploited for bacterial identification, pathogen detection, and biocontrol (Hwang 2014).

It is simpler to develop biosensor surfaces by surface adsorption of phages, though it may give inconsistent results due to unstable immobilization densities (Balasubramanian et al. 2007; Lakshmanan et al. 2007). However, chemically anchoring (cysteamine-modified and glutaraldehyde-activated gold substrate) phages on a detection platform display a consistent improvement in the phage density and detection (Cademartiri et al. 2010; Singh et al. 2013). For chemically functionalizing phage-based biosensors, selection (biopanning) purity of the phage suspension is an important criterion which should be devoid of various other bio-contaminating agents like other carbohydrates, proteins, and lipids (Naidoo et al. 2012). However, genetically modified or engineered phages are more appropriate to develop bio-probes than intact wild-type phages. Being biologically active, wild-type phages upon infection lyse

the host bacterium that may lead to reduction of signal on a biosensor platform (Singh et al. 2010, 2013).

Recently, utilizing unique ability of phages to display peptides or proteins on their surface, called "phage display," is becoming a powerful tool to screen diversity of targets like proteins, carbohydrates, small molecules, or an entire cell. For the phage display technology, lambda, f1, M13, fd, T4, and T7 phages have most widely been used (Smith 1985; Atias et al. 2008; Singh et al. 2013). This emerging technology can revolutionize diagnostics by creating molecules that are otherwise unavailable via conventional approaches. Researchers have successfully expressed cellular proteins and peptides, antibody (or its fragments), and antigen molecule on the surface of phages for developing pathogen detection biosensors, molecular imaging, and gene delivery (Petrenko 2008; Pande et al. 2010; Singh et al. 2013; Hwang 2014; Chuang et al. 2015).

Agriculture and food safety

Phage application in agriculture and food material is an upcoming area of development. *Salmonella*, *Campylobacter*, *Listeria*, and *E. coli* are common bacterial contaminants in food borne-related infections (DuPont 2007). Bacterial infection in crops is a grave problem that reduces the yields (Allen et al. 2011). High resistivity to multiple antibiotics was reported by a number of researchers in the agricultural field (Price et al. 2012; Zhu et al. 2013; Micallef et al. 2013; Popowska et al. 2012). To evade infection, a number of reports of phage application on various crops (like tomato, citrus, and onion) are available (Huff et al. 2005; Lang et al. 2007; Balogh et al. 2008; Jones et al. 2014). Phage products like AgriPhage™, Omnilytics are being used at a large scale for protecting crops from a number of bacterial diseases. Similarly, other phage products like LISTEX (for Listeria sp.; http://www.listex.eu/product/), Listshield™, and Intralytix were approved by the FDA (USA), for treating food products before they are being marketed (Meaden and Koskella 2013). Phages have been exploited to treat colibacillosis and prevent food-borne pathogens (Huff et al. 2005; Sharma et al. 2009). Phage therapy is applicable in restricting bacterial contamination on a variety of food materials like chicken flesh, meat, fruits, and vegetables (Flaherty et al. 2000; Goode et al. 2003; Allwood et al. 2004; Toro et al. 2005; Higgins et al. 2005; Fiorentin et al. 2005; Ravensdale et al. 2007; Sharma et al. 2009; Guenther et al. 2009; Marcó et al. 2012). Further, antimicrobial packaging against the activity of *Listeria monocytogenes* for cantaloupes and ready to eat meat and *E. coli* for alfalfa seeds and sprouts are available in the market (Lone et al. 2016).

Aquaculture industries

Aquaculture industries often undergo economic losses chiefly due to uncontrolled microbial diseases that threaten their development and sustainability (Almeida et al. 2009, Silva et al. 2014). Fish-based products are becoming more popular throughout the world as a cheap source of protein. For the last three decades, considerable growth of aquaculture and related industries has taken place. On the other hand, pathogenic bacteria like *Flavobacterium psychrophilum*, *Photobacterium damselae*, *Vibrio anguillarum*, *Vibrio vulnificus*, *Aeromonas hydrophila*, and *Aeromonas salmonicida* have become more prominent, causing heavy loss and/or diseases in humans due to consumption of contaminated aquaculture products (Subasinghe et al. 2001; Nakai and Park 2002; Flegel 2006; Saksida et al. 2006; FAO Report 2015). Mostly in marine and estuarine fisheries and occasionally in freshwater fisheries, vibriosis is a common disease that causes significant mortality in fish (up to 100 % mortality in larvae). This is also responsible for disease outbreaks in fisheries units. Bacterial genera *Vibrio* (with its various species like *V. vulnificus*, *V. anguillarum*, *V. parahaemolyticus*, *V. alginolyticus*, and *V. salmonicida*) and *Photobacterium damselae* are the causative agents of vibriosis (Noorlis et al. 2011; Higuera et al. 2013; Martínez-Díaz and Hipólito-Morales 2013; Silva et al. 2014). As antibiotic treatments have exhibited reduced effectiveness against multidrug-resistant bacteria, treatments with phages have proven efficient in case of *V. anguillarum* infection in fish larvae (Silva et al. 2014). However, the success of aquaculture phage therapy depends mainly on two factors: number of phages produced by each host cell after host lysis and on latent period for fresh infection to a new host by new phage particles. Ideally, for phage therapy in aquatic condition, maintaining abundant phage number and short period for fresh infection is required, which is a challenge for the days to come (Abedon et al. 2001; Crothers-Stomps et al. 2010; Silva et al. 2014). Table 2 has summarized the phage applicability and trials performed in recent era of antibiotic resistance bacteria.

Wastewater phages and their application in effluent water decontamination

Common wastewater treatment involves technology based on chemical precipitation, ion exchange, sedimentation, or coagulation-flocculation (Otte and Jacob 2006). These techniques are energy and maintenance intensive and require high-infrastructure facilities. Researchers across the world are trying to harness phage-based techniques in wastewater treatments to improve quality of effluent and sludge either released into the environment or reused (Fu and Wang 2011). This treatment has the potential to manage the problems of environmental wastewater processes like: reduction in pathogenic bacteria, foaming in activated sludge plants, digestibility, and water ability of sludge, and reduction in competition between functionally important bacterial populations and nuisance bacteria (Withey et al. 2005; Mulani et al. 2015). This is a highly

Table 2 Representing information on phage therapy trials and its applications in various fields

	Target organism	Disease	Phage used	Phage dose/MOI	Comments/result	Reference
1	*Xanthomonas axonopodis* pv. *Vignaeradiatae*	Bacterial leaf spot of mung bean	XMP^{-1}	6×10^9 PFU/mL	Phage application efficiently provide protection against bacterial infection in mung bean seed	Borah et al. (2000)
2	*Pseudomonas plecoglossicida*	Bacterial haemorrhagic ascites	Phage PPp-W4, PPpW-3	10^7 PFU/g pellets	Oral administration of phage-impregnated feed successfully reduced infection of *Pseudomonas plecoglossicida*	Park et al. (2000)
3	*Salmonella enteritidis*	Contamination of food	*Salmonella enteritidis* specific phages	10^7 PFU/mL	Phage application on fresh cut honeydew melon reduced the bacterial count	Leverentz et al. (2001)
4	*Streptomyces scabies*	Potato scab	AS1	10^9 and 10^{12} PFU/mL	Prior to planting, phage treatment of mother tuber reduced scab lesion coverage	McKenna et al. (2001)
5	Vancomycin-resistant *Enterococcus faecium* (VRE)	Individuals with compromised immune systems are particularly prone to develop VRE infections	Phage ENB6 and C33	3×10^8 PFU/mL	45 min exposure to phage therapy was sufficient to rescue 100 % diseased mice	Biswas et al. (2002)
6	*E. coli*, *Proteus*, *Pseudomonas*, and *Staphylococcus*	Ulcers and wounds	Pyophage	10^6 PFU/cm^2	PhagoBioDerm effectively healed wounds and eliminated causative organism of ulcers in 22 patients	Markoishvili et al. (2002)
7	*Xanthomonas campestris* pv. *Vesicatoria*	Bacterial spot of tomato	Agriphage	10^{10} PFU/mL	PCF and Casecrete formulation of Agriphage increased phage longevity and decreased the pathogen number in field trials	Balogh et al. (2003)
8	*Salmonella enterica* serovar Enteritidis and *Campylobacter jejuni*	Food poisoning	*Salmonella enteritidis* phage type 4 strain P125589, phage 29C phage P22, HTint, *Campylobacter jejuni* phage 12673	MOI:100 to 1000	Bacterial count reduced by 2 log10 within 48 h after phages application (MOI of 100 to 1000)	Goode et al. (2003)
9	*Streptococcus pneumoniae 541, serotype 6B*	Pneumococcal bacteraemia and death	Phage-coded lysins (enzybiotic): Pal amidase and/or Cpl-1 lysozyme	1100 U of Pal amidase or Cpl-1 lysozyme	Phage-coded enzymes successfully protected mice from Bacteraemia after 1 h of phage injection	Jado et al. (2003)
10	*Pseudomonas plecoglossicida*	Bacterial haemorrhagic ascites	Phage PPp-W4, PPpW-3	10^7 PFU/fish	Mortalities of fish reduced and inhibited bacterial infection	Park and Nakai (2003)
11	*Pseudomonas aeruginosa*	Septicemia	Pf3R, Pf3, and Pt1	10^6–10^9 PFU/mL	Pf3R-treated mice showed higher survival rate with reduced inflammatory response	Hagens et al. (2004)
12	*Salmonella enteritidis*	Food poisoning	Phages CNPSA 1, CNPSA3 and CNPSA4	10^9 PFU/mL	Significant reduction in Salmonella count after treating with bacteriophage and found effective lytic action on days 3, 6 and 9 of post-treatment.	Fiorentin et al. (2005)
13	Nonmotile, serotype O2 isolate of *Escherichia coli*	Colibacillosis	*Escherichia coli* phages SPR02 and DAF6	DAF6, 10^9 PFU/mL; SPR02, 10^8 PFU/mL	Phage therapy successfully recovered *E.coli* infection in birds after 24 or 48 h	Huff et al. (2005)

Table 2 (continued)

	Target organism	Disease	Phage used	Phage dose/MOI	Comments/result	Reference
14	*Vibrio harveyi*	Mass mortalities of shrimp larvae	Vibrio harveyi specific phage	10^9 PFU/mL	Bacteriophage treatment enhanced larval survival by (80 %) as compared control (25 %)	Vinod et al. (2006)
15	*Staphylococcus aureus strain 2698*	Wound and soft-tissue infection	LS2a	10^9 PFU/mL	Treatment of wound infection by *Staphylococcus aureus* phages prevent formation of abscess in rabbit model	Wills et al. (2005)
16	*Aeromonas salmonicida HER 1107*	Furunculosis	Bacteriophage HER 110	10^9 PFU/mL	In brook trout, bacteriophage application delayed furunculosis onset by 7 days	Imbeault et al. (2006)
17	*Aeromonas salmonicida* subsp. *Salmonicida*	Furunculosis of Atlantic salmon	*Aeromonas salmonicida* phages O, R, and B	10^5, 10^7, and 10^8 PFU/fish	Slow down the mortality rate, but at the end 100 % mortality was reported	Verner-Jeffreys et al. (2007)
18	*Vibrio harveyi*	Mortality of Penaeus monodon larvae	Bacteriophage specific to *Vibrio harveyi*	10^6 PFU/mL	85 % increase in survival at larval stages of shrimp	Karunasa gar et al. (2007)
19	*Xanthomonas axonopodis* Pv. Allii	Xanthomonas leaf blight of onion	Agriphage	10^8, 10^7, 10^6, or 10^5 PFU/mL	Biweekly or weekly applications of bacteriophages under green house condition reduced leaf blight disease by 26 to 50 % and proved equally better as weekly applications of copper hydroxide plus mancozeb	Lang et al. (2007)
20	*Pseudomonas aeruginosa strain D4*	Septicemia in immunocompromised hosts	KPP10	10^{10} PFU/mL	Oral administration KPP10 significantly reduced gut-derived sepsis caused by *P. aeruginosa*	Watanabe et al. (2007)
21	*Xanthomonas axonopodis subspecies citri* and *citrumelo*	Citrus canker and Citrus bacterial spot	CP2, ΦXac2005-1, ccΦ7, ccΦ13, ΦXacm2004-4, Xacm2004-16, ΦX44, and ΦXaacA1	10^6, 10^8, 10^9, and 10^{10} PFU/mL	Treatment of sensitive Valencia oranges with bacteriophage provided significant disease reduction in plants	Balogh et al. (2008)
22	*Pseudomonas aeruginosa* and *Staphylococcus aureus*	Burn wound patients	Bacteriophage cocktail PNM, 14/1 and ISP	10^9 PFU/mL	Bacteriophage cocktail found effective in treating burn wound and is being evaluated in a pilot clinical study cleared by Medical Ethical Committee	Merabishvili et al. 2009
23	*Escherichia coli O157:H7*	Watery diarrhea, hemorrhagic colitis, hemolytic uremic syndrome, and in some cases death	Bacteriophages e11/2 and e4/1c	10^{11} PFU	Bacteriophages e11/2 and e4/1c effectively reduced the number of *Escherichia coli O157:H7* in Rumen model	Rivas et al. (2010)
24	*Ralstonia solanacearum*	Bacterial wilt	RSA1, RSB1, and RSL1	10^9 PFU/mL	In tomato seedlings, application of phage ϕRSL1 prevents bacterial wilt	Fujiwara et al. (2011)
25	*Klebsiella pneumoniae B5055*	Burn wound infection	Phage Kpn5	MOI:200	Kpn5 phages have therapeutic importance in treating burn wound infection in mice	Kumari et al. (2011)
26		Columnaris		10^5–10^9 PFU/mL		Laanto et al. (2011)

Table 2 (continued)

	Target organism	Disease	Phage used	Phage dose/MOI	Comments/result	Reference
	Flavobacterium columnare		Flavobacterium phages (a) FCV-1, (b) FCL-2, (c) FJy-3, (d) FKo-2, and (e) FKy-1		Flavobacterium phages were found more host specific to *F. columnare* and can be useful in treating Columnaris in fishes	
27	*Dickeya solani*	Rotting and blackleg of potato	T4-related Bacteriophage (vB_DsoM_LIMEstone1 and vB_DsoM_LIMEstone)	10^{10} PFU/L	Phage application on infected tubes resulted in a higher yield potato tubers	Adriaenssens et al. (2012)
28	*Pseudomonads aeruginosa*	Infections of MDR *Pseudomonads aeruginosa*	Phage PS5	~9×10^8 PFU (First dose) ~3×10^8 PFU (Second dose)	In murine model treatment with Phage PS5 resolved the infection of MDR *Pseudomonads aeruginosa*	Golkar et al. (2013)
29	*Vibrio anguillarum*	Vibriosis	KVP40 and (Phages H1, H2, H4, H5, H7, H8, H20, and 2E-1, S4-7, and S4-18)	MOI: 0.1, 1, and 10	Lytic phages were identified against *V. anguillarum* hosts to treat Vibriosis	Tan et al. (2014)
30	*Escherichia coli* (Antibiotic-resistant clinical strain)	Wounds	TPR7	10^{10} PFU/mL	Phage administration in animal cured from infection after 48 h and results were equally effective as found in the group treated with gentamicin.	Rahmani et al. (2015)
31	*E. coli strain DPC6051*	*E. coli* infections	APCEc01, APCEc02, and APCEc03	MOI 10^{-3} and 10^5	Phage cocktail reduced biofilm formation and effective in preventing the appearance of phage-resistant mutants	Dalmasso et al. (2016)
32	*Pseudomonas aeruginosa*	Pseudomonas infections	Phage KTN4	MOI 100	KTN4 phage injection in Galleria larvae model inoculated with *P. aeruginosa* strains successfully reduced colony count (4–7 log) of *P. aeruginosa*	Danis-Wlodarczyk et al. (2016)
33	*Escherichia coli (ETEC) K88*	ETEC infection in post-weaning pigs	Phages against enterotoxigenic *Escherichia coli* (ETEC) K88	10^7 PFU/kg	Treatment with phages was found effective for reduction of acute ETEC K88 infection in post-weaning pigs	Lee et al. (2016)
34	*Escherichia coli* and *Klebsiella pneumoniae strains*	Urinary tract infections	Pyo, Intesti, Ses, Enko bacteriophages, 29 *E. coli*, and 10 *K. pneumoniae* bacteriophages	10^7 PFU	Lytic action of commercial bacteriophage cocktails on *E. coli* and *K. pneumonia* strains isolated UTIs patients	Sybesma et al. (2016)

potential area of research and development especially in a country like India; there is potential here for application of appropriate, affordable, sustainable, and eco-friendly approaches. Phage-mediated bactericidal effects in any wastewater treatment process have many controlling factors that lead to treatment performance. Wastewater is rich in microbial diversity that contains a wide variety of microbes and bacteriophages, among which, somatic coliphages are the most abundant. These coliphages are virulent, in nature, generally following lytic cycle for their reproduction. These phages belong to the families Myoviridae, Siphoviridae, Podoviridae, and Microviridae that mainly target the member of *Enterobacteriaceae* family especially *E. coli* (Hayes 1968). Coliphages find favorable environment in wastewater. However, their abundance depends upon factors like optimal condition and density of the host bacteria, pH, temperature, cations like calcium and magnesium, organic matter concentration, etc. (Grabow 1990; Grabow et al. 1980, 1998). For instance, fecal coliform bacteria closely related to *E. coli*, especially *Klebsiella* species, are heterotrophic and favor certain water environments for its multiplication and in turn support the multiplication of somatic coliphages (Grabow et al. 2000). It has been reported that phage titer against *Salmonella typhi* in both laboratory media and sewage was found to be 10^9–10^{10} per milliliter (Goyal et al. 1980). Successful phage replication requires a minimum of 10^4 host bacteria per milliliter. According to Goyal et al. (1987), phages under nutrient-limited conditions were found concentrated on the solid surface instead of flowing water. Coliphages also inhabit inside the gut of humans and other warm blooded animals, multiply within it, and are excreted along with fecal matter. Different pieces of information are available on phages in sewage. A number of studies have reported density of somatic coliphages to be 10^6–10^8 per milliliter (Bell 1976; Ignazitto et al., 1980; Havelaar and Hogeboom 1984; Havelaar et al. 1984; Tartera et al. 1989; Grabow et al. 1993; Grabow et al., 2000).

Interestingly, some members of coliphages showed similarity with human viruses like enteroviruses such as polio viruses (Family Picornaviridae) and F-RNA coliphages (Family Leviviridae) (Kamiko and Ohgaki 1993). Both viral particles consist of an icosahedral capsids (about 25 nm diameter) and a single strand (ss)-RNA genome. Due to these similarities, coliphages are considered to be valuable models or surrogates for human enteric viruses (Grabow 2001), which are also excreted along with fecal matter (Grabow et al. 1995). Although coliphages are shed regularly along with fecal matter, human enteric viruses are excreted generally during infection. Greater number of adenoviruses than enteroviruses have been constantly present in raw sewage around the world (Irving and Smith 1981; Hurst et al. 1988; Krikelis et al. 1985a, b), and according to Hurst et al. 1988, 80 % of infectious adenoviruses shed in the feces and present in raw sewage may be enteric adenoviruses. Recently, human fecal contamination was indicated using potential source indicators such as bacteriophages against Bacteroides (GA-17, GB-124, and ARABA 84) as well as sorbitol-fermenting Bifidobacteria (Wicki et al. 2015). Furthermore, according to Haramoto et al. (2015), coliphages belonging to the genogroup, GI F-RNA, may be used as a suitable indicator of virus reduction during wastewater treatment.

Impediments of phage application: interplay between phage and bacterial resistance

There is a tug of war between phage and bacterial infection and immunity. The selective pressure among these two entities is unique. Bacteria develop resistance to phage; subsequently, phages improve their antiviral mechanism and vice versa. This interplay between phage and bacteria is an interesting phenomenon; elevated mutation rates is a normal event for bacteria like *Pseudomonas fluorescens* when they are subjected to coevolve in the invitro systems (Buckling and Rainey 2002). Again, Pal et al. (2007) showed that in laboratory conditions, coevolution of *P. fluorescens* with its bacteriophage help in faster bacterial mutation rates. They have also found that 25 % of the *P. fluorescens* populations (approx. 200 bacterial generations) coevolving with the lytic phages had evolved 10 to 100-fold increase in mutation rates (Pal et al. 2007). For lytic bacteriophages, reciprocal selection for bacterial resistance and phage infectivity is essential. And this bacteria-phage interface generates more beneficial resistance mutations to the bacteria (Gomez and Buckling 2013). However, natural populations of the bacteria-phage coevolving in their natural environment (as for example, soil) may not follow the same mutation pattern as, in nature, several other factors may influence the selection rates for mutation. Innumerable microbial species including natural microbial and viral community (NMC) as a whole and other physico-chemical factors possibly will influence the rate of mutation (Gomez and Buckling 2013).

Bacterial resistance towards phage, therefore, may be due to several mechanisms. These include modification of phage attachment or adsorption sites (receptors) and CRISPR sequence-based adaptive immunity (Hyman and Abedon 2010). Alteration of phage adsorption sites/receptors is the most common phenomenon by which bacteria evade phage infection and become resistant to phage. However, phages can also adapt themselves to recognize these new modified receptors. Synthesis of exopolysaccharide (EPS) or masking proteins (like protein A of *S. aureus*) to mask the phage receptor is another strategy of bacteria. Again, phages conquer the barrier by cleaving the EPS layer using polysaccharide lyase or a polysaccharide hydrolase (Labrie et al. 2010, Örmälä and Jalasvuori 2013).

Further, self/non-self discrimination in prokaryotes is ubiquitous and provided by restriction-modification (RM) systems that defend hosts from exogenous DNA (Pleška et al. 2016). Bacterial system has the ability to recognize and modify the phage DNA. In many instances, the phage DNA is cleaved by the restriction endonucleases on entering into the bacterial cell through RM system and protects bacterial cell from foreign phage DNA attack (Pleška et al. 2016).

It has also been reported that phages adopt anti-restriction strategy to avoid recognition by endonuclease enzyme. For example, T4 phage escapes of restriction endonuclease attack as it contains hydroxymethylcytosine (HMC) instead of cytosine. However, some bacteria, again, modified their system to specially recognize hydroxymethylcytosine (HMC) and shatter phage DNA (Bickle and Kruger 1993; Borgaro and Zhu 2013). Yet again, anti-restriction strategy in *Staphylococcus* phage *K* is interesting where no 5′ GATC-3′ cleavage site is present; hence, DNA is protected from restriction (Kruger et al. 1988; Tock and Dryden 2005, Bryson et al. 2015).

CRISPER-Cas mechanism or Clustered regularly interspaced short palindromic repeats (CRISPRs) and the CRISPR-associated (cas) genes present a novel example of acquired resistance against viruses in prokaryotes. This mechanism is widely present in genome of bacteria and archaeal population and CRISPER-Cas loci were first described in 1987 in *E. coli* (Ishino et al. 1987). CRISPER is composed of 21–48 bp direct repeats separated by (26–72 bp) non-repetitive spacers, and at 5′ edge, this loci is flanked by a number of *cas* genes (4–20 in number) in bacterial strains. The variation in cas gene and spacer make this system more unique and robust (Marraffini 2015). Main function of CRISPER-Cas is to provide immunity against foreign DNA including phage genomic DNA or plasmid DNA (Makarova et al. 2006; Bolotin et al. 2005; Haft et al. 2005; Mojica et al. 2005; Pourcel et al. 2005; Marraffini and Sontheimer 2008). Further, as for example of antiphage activity of CRISPER-Cas mechanism in *Streptococcus thermophilus*, exposure to virulent phage gave rise to the phage-resistant mutants due to insertion of additional 30 bp spacer similar to protospacer of infecting phage (Barrangou et al. 2007). The event of acquiring immunity against phage can be explained in following steps like adaptation or spacer attainment, transcription of acquired spacer (small CRISPER RNAs (crRNAs), on recurrent phage attack this crRNAs form a complex with Cas protein), and immunity against phage (crRNAs-Cas complex direct nuclease to trace and chop the invading phage DNA; Marraffini 2015).

Conclusive remarks

Phages are omni-present, ubiquitous, and important part of nature. Being antibacterial and natural predators of bacteria, the role of phage can be extensive as nano-cleaner of ecosystem. Detailed classification of bacteriophages may be beneficial to mankind in the screening of therapeutic phages against a number of diseases and economically important phages help in industries and its preservation. High-throughput sequencing like metagenomics study of environmental samples can provide information of novel bacteriophages or new bacteriophage species. Various biological, environmental, medical, and pharmaceutical applications related to the use of phage are becoming more and more attractive. Further, employability of phage for sustainable wastewater treatment is a challenging approach. Labeled phages are used in situ bacterial detection using phage typing of clinical bacterial strains. Although discovered a century ago, their use in various fields are still restrictive. Comprehensive studies on basic molecular biology, host range increment, and genetics processes of these tiny antibacterial agents are required which will help them consider novel beneficial agent for bactericidal activities, even against multidrug-resistant bacteria.

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