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Bacteriophages of the Lower Urinary Tract

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Abstract

The discovery of bacteria in the female urinary bladder has fundamentally changed current dogma regarding the urinary tract and related urinary disorders. While prior research has characterized many of the bacterial components of the female urinary tract, the viral fraction of this community is largely unknown. Viruses within the human microbiota far outnumber bacterial cells, with the most abundant viruses being those that infect bacteria (bacteriophages). Similar to observations within the microbial communities (microbiota) of the gut and oral cavity, preliminary surveys of the urinary tract and bladder microbiota indicate a rich diversity of uncharacterized bacteriophage (phage) species. Phages are vital members of microbiota, playing critical roles in shaping bacterial metabolism and community structure. Here, we review the current knowledge of phages within the urinary tract and their possible contribution to urinary tract health. Furthermore, as the natural predators of bacteria, phages have garnered renewed interest in their use as antimicrobial agents. Both historical and recent applications of phage therapy for lower urinary tract infections and other disorders are discussed.

The Bladder Microbiome

The Human Microbiome Project (HMP) revolutionized our understanding of bacteria that inhabit the human body [1]. The bladder, however, was not included in the HMP publications, which focused on the oral cavity, nasal cavity, skin, gastrointestinal tract, and vagina [1,2]. In the absence of a urinary tract infection (UTI), it was long thought that the bladder was sterile [3]. This dogma resulted, in part, from the wide use of standard clinical microbiology urine culture protocols, which are designed to detect common fast-growing pathogens with basic nutrient needs and no aversion to oxygen (especially *Escherichia coli*). Thus, the standard protocol does not detect anaerobes, slow growers, or bacteria with complex needs. Using an enhanced urine culture method called expanded quantitative urine culture (EQUC) and/or DNA sequencing methods, diverse bacterial and fungal species have been detected in standard culture-negative urine obtained directly from the bladder via transurethral catheterization (herein catheterization) or suprapubic aspiration [4–12] (for a review, see Whiteside et al. [13]). These and other studies of the bladder microbiome and microbiota have revealed associations of bladder bacteria with post-operative UTIs [14,15], urgency urinary incontinence (UUI) [8,9,11], and response to overactive bladder treatment [16]. Some bacteria are

even associated with the lack of symptoms and protection against post-instrumentation UTI [8–10]. These results suggest that the bladder may possess its own protective microbiota and that dysbiosis results in disorders, e.g. UTI and UUI (for recent reviews, see Brubaker & Wolfe [17]; Mueller et al. [18]). A recent effort to generate a genomic catalogue of bacteria isolated from the bladder has revealed that the genomes of bladder bacteria are quite distinct from bacteria isolated from the gut, but somewhat similar to those of the vagina [19].

Viruses and the Human Microbiome Project

Although the HMP focused on characterizing the bacterial fraction of the human microbiota, sequencing of some viral genomes was unavoidable, both because viral DNA was present in the samples and because prophage DNA was present within the bacteria [20]. Subsequent to the original initiative, bacterial and viral communities within the five niches studied in the HMP have been extensively investigated (for a review, see Lloyd-Price et al. [21]), most notably the communities inhabiting the gastrointestinal tract. These viral communities include both eukaryotic viruses as well as viruses that infect bacteria or bacteriophage (phage). The gut virome (viral component of the microbiome) has been the focus of numerous studies [22–27] (for a review, see Manrique et al. [28]), each leading to the same conclusion: phages are key members of the gut's microbiota. Within the gut of healthy individuals, there exists a core phage community [27] and disruption of this core phage community (dysbiosis) has been associated with certain GI symptoms and disease [24,26–29]. Most recently, seven phage taxa within the gut were found to be associated with type 2 diabetes, establishing a type 2 diabetes-specific gut phage community [30]. Other studies have characterized the viromes of the other body sites from the HMP [31–36]; the data from these studies are publicly available (Table 1). Like the gut, studies of these other body sites have identified associations between phage communities and patient symptoms/disease. For example, phage within the oral cavity have been linked to periodontitis [33]. In contrast with the sites of the HMP, investigation of the phage communities has only recently begun.

Bacteriophages

Phages are ubiquitous viruses that infect bacteria; they are the most abundant biological entities, far exceeding even bacteria. Surveys of the marine environment have led to an estimated 10^{30} phages in the oceans alone, representing roughly 10 phages for each bacterial cell [37]. In addition to their abundance within the marine environment [38], phages are prevalent within the soil [39,40] and freshwater [41]. They have even been isolated from some of the most inhospitable conditions, including desert sands [42], sea ice [43], and the depths of the ocean [44]. In addition to our surroundings, phages are abundant in and on plants [45] and within the bodies of insects and mammals [46,47]. Indeed, the human gut alone is home to an estimated two trillion phages [48], greatly exceeding the number of eukaryotic viruses in our bodies [49]. Although phages are unable to infect eukaryotic cells, there is evidence of direct interactions between phages and human cells [50,51]. However, the full extent of direct and indirect effects of phages can only be imagined, as researchers have only just begun to explore the roles of phages in the human body, including the human immune and central nervous systems (for a review, see Barr [48]).

There are three distinct, generally well-characterized life cycles for phage propagation and reproduction: lytic, lysogenic and chronic. All phages infect their bacterial host by binding to surface receptors, a process called adsorption (Fig. 1); these receptor binding proteins are often quite specific, leading to a narrow range of hosts (strains or species) that a particular phage can infect (see discussion in Koskella & Meaden [52]). Following adsorption to the host cell, the phage injects its DNA or RNA genome into the host's cytoplasm. In the lytic cycle, the phage genome replicates and phage proteins are synthesized. For dsDNA phages, DNA is inserted into the protein procapsid, while for ssDNA and ssRNA phages, the capsid is formed around the nucleic acid (Fig. 1). The bacterium's cell wall breaks ("bursts") (for a review, see Young [53]), and the phage progeny disperse into the surrounding environment. While some phages are obligately lytic, others, called temperate, can alternate between the lysogenic and lytic cycles. In the lysogenic cycle, the phage genome is either integrated into the host genome or remains in the cytoplasm as a self-replicating plasmid [54] (Fig. 1). The phage genome (now called a prophage) generally replicates in synchrony with the host chromosome. Temperate phages, such as the model phage λ, are capable of going through the lytic and lysogenic cycles. Their prophages can remain dormant for generations until, often, an environmental cue, such as host starvation, change in nutrients, temperature [54,55], triggers entry into the lytic cycle – a process known as induction. This decision between the lysogenic and lytic cycle can also be determined by the recently reported phage-produced peptide communication system (the 'arbitrium' system), in which progeny phage lysogenize when this small-molecule is abundant within the environment [56]. In addition to the lytic and lysogenic cycles, phages can reproduce by chronic infection; phages are shed from the bacterial cell without killing the host cell, e.g., the filamentous phage M13. While the majority of known phages can be associated with one of these three life cycles, additional modes of infection and reproduction have been described [55,57,58].

Given these multiple mechanisms of infection and persistence, it comes as no surprise that phages can have profound effects on microbial communities (Fig. 1). Phages can transform the microbial community through predation (lysis) [59–61]. Furthermore, phages can drive bacterial diversity within a community [62–65], including adaptation in susceptible host species, e.g. loci associated with phage-resistance [66,67]. Exposure to temperate phages can increase bacterial virulence (a process referred to as lysogenic conversion) [68,69] by, for example, encoding for toxins [70,71]. Case reports detail shiga toxin (Stx)-producing *E. coli* strains, most commonly associated with enteric infections, found within the urine of individuals with UTIs [72–74]. Thus, lysogeny can be beneficial for the bacterial host (for a review, see Harrison & Brockhurst [75]). Because they integrate their genome into their host's genome, some temperate phages can transfer genetic material from one cell to another (transduction); this process can benefit the recipient host cell. Indeed, temperate phages are well known to mediate horizontal gene transfer (HGT) and have helped spread virulence and/or resistance factors through bacterial communities (for a review, see Touchon et al. [76]). Similarly, lytic phages can also transfer bacterial DNA [77]. Data exists that support both frequent and infrequent phage-mediated spread of antibiotic resistance genes [78–81]. Phage also can contribute to HGT indirectly; a recent study identified two superspreader phages [82]. In this scenario, phage lysis spreads intact host plasmids, enabling HGT via transformation. Given the large genetic diversity present within phage communities [83], we have only begun

to scratch the surface of the complexities of phage-host dynamics [84–86] (for a review, see Manrique et al. [28]).

As phage genomes can be dsDNA, ssDNA, dsRNA, or ssRNA, linear or circular, and even segmented, sequencing phage populations often is limited by the genomic nucleic acid extraction protocol and may necessitate amplification prior to sequencing (for a review, see Hayes et al. [87]). Nevertheless, whole genome sequencing technologies have enabled researchers to identify new phage species. In contrast to cellular organisms, there is no universal marker for phages because no gene is conserved within all phages. To identify phages, researchers often target genes that encode structural proteins as phylogenetic markers [88]. These signature sequences, however, are far from comprehensive [89]. Only a small fraction of phage sequence diversity is represented in extant sequence databases, and it is heavily biased for sequences of phages with DNA genomes that infect bacterial species routinely studied in the laboratory [84,90,91]. Metagenomics has allowed us to explore the diversity of phages on Earth. Later in this review, we will take a closer look into the viral metagenomic studies of the lower urinary tract.

Viruses of the Urinary Tract

The urinary tract harbors a diverse eukaryotic viral community, including Adenoviruses, Anelloviruses, Papillomaviruses, and Polyomaviruses. Adenoviruseses can be detected in urine [92], and can range from limited, localized infections in otherwise healthy individuals to severe and potentially fatal infections in immunocompromised individuals (for a review, see Lion [93]). Torque teno virus (TTV), also referred to as small anellovirus, has largely been studied in relation to immunodeficiency in transplant recipients (for a review, see Tan et al. [94]). In the study of Rani et al. [95], mid-stream clean catch urine was collected from 22 kidney transplant recipients; whole genome sequencing was conducted for these urinary viromes and 108 different types of TTV were detected. The most prevalent eukaryotic virus in urine samples is human polyomavirus 1 (BK virus) and 2 (JC virus) [96]. While both polyomaviruses appear to have little effect on healthy individuals, each can lead to nephropathy and hemorrhagic cystitis in immunocompromised populations (for a review, see Hirsch et al. [97] and Rinaldo et al. [98]). Recently, we conducted metagenomic sequencing of the bladder microbiome (bacterial and viral fraction) of 30 individuals and were able to reconstruct the full JC virus genome in five of these samples [99]. JC virus and other polyomaviruses have similarly been detected in other viromes from urine samples (obtained by an undescribed voided urine collection method) [100]. Human papillomaviruses (HPV) also have been detected in voided urine [101] and bladder tissue [102,103]. While certain HPV genotypes have been attributed to condylomata acuminatum of the bladder [104,105], these high-risk genotypes are rare. In one investigation of the urinary virome, 95% of the 20 subjects sampled included HPV sequences [106]; for eight patients, these samples were collected via intermittent catheterization, and the others via an undescribed voided urine collection method. It is, however, estimated that eukaryotic viruses represent just a small fraction of the urinary virome [99,100,106,107].

Lytic phages have been isolated directly from urine on numerous occasions. In fact, the seminal work of the co-discoverer of bacteriophages, Félix d’ Hérelle, first isolated a phage

from urine. While d' Hérelle may not have known exactly what a phage was, this invisible microbe lysed the Shiga bacillus [108]. A century later, two studies isolated phages capable of infecting *Pseudomonas aeruginosa* from urine samples [109,110]. Transmission Electron Microscopy (TEM) of the isolated phages provided clues into the phages' morphology, which includes a tailed siphophage [109] and two tailless phages [110]. Our group has isolated a fourth *Pseudomonas*-infecting phage, induced from a bacterial isolate from a urine sample collected via catheterization (Johnson et al., in preparation). This phage is capable of lysing *P. aeruginosa* PAO1. Coliphages, or phages that infect *E. coli*, also have been isolated from voided and catheterized urine samples. From the routine plating of a patient's urine sample (collection method unknown), Dallas & Kingsbery [111] found 100,000 CFU/ml of bacterial growth and, upon closer inspection, plaques. Four coliphages were isolated from clinical urine samples and their morphologies were determined (via TEM) to be siphophages [109]. We isolated an additional seven coliphages from the bladder (from urine collected via catheterization) of four women with UUI [112]. From the complete genomes of these seven coliphages, six resemble coliphages isolated from cattle slurry [113], while the sequence of the seventh (phage Wrath) most closely resembles a lysogenic *Bacillus* phage sequence. TEM images, including that in Fig. 2 for the coliphage Greed, also suggests the morphology of siphophages. The host-range of Greed was recently tested [114]; in addition to its ability to lyse the laboratory strains *E. coli* C and K-12, it is also capable of infecting and lysing some *E. coli* strains isolated from urine samples, including the uropathogen *E. coli* CFT073.

The lytic phage population, however, includes but one part of the phage community within the bladder; recent evidence suggests that lysogenic phages are dominant within the gut microbial community [115]. Within *E. coli* isolates from the bladder, several prophages have been identified [116]. Although a lytic *Gardnerella*-infecting phage has yet to be isolated, numerous prophage sequences were identified within the genomes of four *Gardnerella* strains isolated from urine specimens obtained via catheterization from the bladders of adult women with UUI [117]. Analysis of these four genomes and other publicly available *Gardnerella* genomes revealed that phage infections were pervasive within the urinary microbiota [117]. We next expanded this examination of lysogenic phages to include 181 bacterial isolates, representative of the phylogenetic diversity within the bladder [118]. These samples were collected from women both with and without lower urinary tract symptoms. Over 400 phage sequences were identified; the majority (86%) of these bacterial isolates harbored one or more lysogenic phages [118]. Furthermore, many (57%) of the phages identified in this study [118] exhibited no sequence similarity to any known phages, indicative of a vast unexplored phage population residing in the bladder.

To date, three published studies have employed a metagenomic approach to sequence the viral fraction of the urinary microbiota. The first study, conducted by Santiago-Rodriguez et al. [106], sought to determine whether the urine viral community was affected by urinary tract health status. The viral fraction (eukaryotic viruses and extracellular phages) of urine collected from 10 individuals with and 10 individuals without a diagnosed UTI were sequenced. For each cohort, samples were collected either via catheterization or voided urine from five males and five females. Only 27% were homologous to known viruses, the majority of which represented phage genes [106], again hinting at a large unexplored phage community within the urinary tract. While the subsequent study of Thannesberger et al. [100]

also found a large phage community, they concluded that the phage community primarily consisted of relatives of known species, the majority resembling Chlamydiamicroviruses, which infect *Chlamydia* spp. This study included two healthy individuals and four individuals with human cytomegalovirus (CMV) infections. However, information about how the urine was collected or demographics for the patients was not provided. The third published virome study sequenced urine samples collected (via the voided mid-stream clean catch method) from 14 male and eight female kidney transplant patients [95]. While phages are likely present in these samples, this study did not mention phages and sequence data is not publicly available; instead, the authors focused solely on eukaryotic viruses.

Viral diversity within the urinary tract also has been studied by sequencing the entire urinary microbiome. Moustafa et al. [107] recently published a study in which metagenomic sequencing was performed for the urinary microbiome of 49 individuals (collected via clean-catch). As this study did not select for the viral fraction, most of the sequenced data corresponded to bacterial genetic material. Nevertheless, viral – primarily phage – sequences were detected [107]. Like the study conducted by Santiago-Rodriguez et al. [106], this study also examined samples from individuals with UTIs and detected sequences homologous to those from phages that infect bacteria commonly found within the urinary tract and associated with UTIs, including *Escherichia*, *Enterococcus*, *Lactobacillus* and *Pseudomonas* [107]. We recently took a similar approach, sequencing urine collected by catheterization from 10 asymptomatic women and 20 women with overactive bladder. Partial and complete viral genomes were reconstructed in 12 of the 30 samples sequenced, including the complete genomes of novel phage strains [99]. Partial and complete phage genomes also exhibited sequence homology to previously characterized lytic or lysogenic phages that infect *Gardnerella*, *Lactobacillus*, and *Streptococcus* spp. In sequencing both the bacterial and viral members of the microbiota, associations between phages and their hosts can be inferred.

Challenges of Studying Phages in the Bladder

In contrast to the microbiota of the GI tract, oral cavity or vagina, the bladder has orders of magnitude less microbial biomass [7,119,120]. DNA concentrations are often low, a challenge faced by both those studying the bacterial and viral constituents of the bladder [121]. Thus, two of the metagenomic studies of the urinary virome employed amplification prior to sequencing [100,106]. While efficient in increasing viral genomic material, these amplification methods have well documented biases [122]. Perhaps of greater concern is the method in which urine is collected and the community the collected urine represents. In a previous work [5], the bacterial communities obtained via catheterization and suprapubic aspiration from women were compared, finding that both methods: (1) did not resemble the skin or vaginal microbiomes and (2) successfully avoided vulvo-vaginal contaminants. The method of urine collection is a frequently debated and investigated topic in the field [17,121,123], balancing invasive procedures during collection and the purity of the sample obtained. This debate is not unique to the bladder, urinary tract, or urine; biopsies and stool samples present quantitatively and qualitatively different stories for the gut [124] and methods for sampling the gut microbiota are still being refined [125,126]. Studies of voided urine have routinely observed vaginal contamination of clean-catch samples [12,107]. The virome studies of Santiago-Rodriguez et al. [106], Rani et al. [95], and Moustafa et al. [107] investigated voided urines either

partially or entirely (in the case of the last two studies). Thus, it remains unknown if the viruses detected reside in the bladder and/or in/on the urethra, vagina, or skin. In contrast, catheterized urines have a lower probability of contaminants [127]. Study of less invasive methods for collection is an ongoing pursuit [128]. Until a less invasive method can be determined, investigations of the bladder virome should use urine obtained by catheterization or suprapubic aspirate.

Phages and Urinary Tract Health

Associations between phage communities, bacterial populations, and the human host are open questions within the field. Recent studies suggest that phages may contribute to human health [129], in particular the gut [24,26–29]. These studies of the gut will likely illuminate studies of the bladder and other niches of the human body. Evidence has emerged recently suggesting a similar association between phage communities and bladder symptoms. We observed variation in the abundance of lysogenic phages in bacteria isolated from asymptomatic individuals and those with overactive bladder [118]. Variation, determined via the beta diversity statistic and principle component analysis, was not detected in the extracellular phage populations of individuals with and without UTI symptoms [106]. However, it is important to note that, in contrast to the gut phage communities, our understanding of the diversity of phages within the urinary tract has only just begun. Cataloguing the phage community in both asymptomatic and symptomatic individuals is a critical first step in understanding if and how phages contribute to urinary tract health. Further investigation of the phage-bacteria dynamics of the bladder and urinary tract could reveal indicators for early detection of symptoms.

Phages also may offer a defense to the human host. Studies of the gut communities have revealed unexpected ways in which phages interact with human cells, organs, and immune system. The prevalence of phages within the mucosal surfaces of the gut may confer a direct benefit to the human host, protecting the epithelium from bacteria [130]. Recent evidence suggests that phages are in fact more virulent to bacteria when human cells are present [131]. Furthermore, phages can interact directly with human cells. Studies have found that phages can bind to cancer cell membranes and inhibit or attenuate tumor growth [132]. Although phages cannot infect eukaryotic cells, they can enter eukaryotic cells. A phage may be a stow-away, as a cell of an invasive bacterial species that harbors a phage could enter a eukaryotic cell [133,134]. Alternatively, eukaryotic cells can take up free phages by endocytosis [133]. A recent study showed that phages are capable of penetrating epithelial cell layers with an estimated 31 billion phage particles passing through these layers of the gut into the body daily [51]. Within the human body, phages can modulate immune responses (for a review, see Górski et al. [135]). Evidence includes phage-mediated inhibition of *in vitro* T-cell proliferation [50] and stimulation of humoral responses in mice [136]. While the future of phage-mediated immunoregulation holds promise, the mechanisms by which phages interact with the immune system remains largely unknown.

There is growing appreciation of the therapeutic potential for modulating the human microbiome. Induction and release of temperate phages can lyse sensitive competitor strains or lysogenize other cells [137,138]. Alternatively, an individual's bacterial infection can be

treated with obligately lytic phages, known as phage therapy. In the face of the increasing threat of antibiotic-resistant bacterial strains, phage therapy has regained interest (for a recent perspective, see Lin et al. [139]). Phage therapy was a promising area of UTI treatment in the early 20th century. For instance, in a 1928 report, phages isolated from sewage were 90% efficient in lysing bacteria causing UTIs [140]. While the US and Western Europe abandoned phage therapy when antibiotics became commercially available (amongst other reasons) [141], this area of research and treatment continued in Eastern European countries. Phage therapy is a publicly available treatment for individuals with UTIs in these countries. Within the scientific literature, in one study [142],41 *E. coli* and 9 *Klebsiella pneumoniae* strains isolated from individuals with UTIs were challenged with phages from collections from the Democratic Republic of Georgia. Only one *E. coli* isolate was resistant to the individual phages and phage cocktails tested, and one phage was capable of lysing all *K. pneumoniae* strains. Similar efficiencies have been observed for other bacterial species that cause UTI symptoms. A single patient, for whom antibiotics were unable to clear the root cause of the UTI -*P. aeruginosa*, was successfully treated with phages [143]. A 2-year clinical trial recently concluded, and while results are not yet published, patients with UTIs were treated with either a bacteriophage, an antibiotic, or a placebo [144] (https://clinicaltrials.gov/ct2/show/NCT03140085). Phages have also been explored for their potential use in treating long-term catheters to minimize bacterial biofilm development and catheter blockage, which can cause catheter-associated UTIs (CAUTIs) (for a review, see Siddiq & Darouiche [145]) in addition to chronic bacterial prostatitis (for review, see Letkiewicz et al. [146]). Nevertheless, a better understanding of phage, microbiota, and human host interactions is imperative for the feasibility of phage therapy in Western medicine.

Conclusions

While whole genome sequencing and new enhanced culture methods have greatly benefited the study of the microorganisms within the bladder and the rest of the lower urinary tract, significant work remains. Although the literature reflects an ongoing debate surrounding the potential presence of vulvo-vaginal and/or skin bacterial contaminants in urine samples, here we begin the same conversation relative to the study of the virome. Most of the studies discussed here, with a few exceptions [106,112,117,118], have used voided urine for isolation of lytic phages or sequencing of the urinary virome. To the best of our knowledge, the phage populations of adjacent anatomical locations have yet to be investigated. As we have just begun to explore the phage communities within the urinary tract, such considerations must be kept in mind. More samples must be sequenced to determine if, like in the gut [27], a core phage community exists within the bladder, the urethra, peri-urethral and adjacent urogenital niches. Only through such efforts can we fully ascertain what a healthy and unhealthy community looks like. Is a shift from a lysogenic to a lytic lifestyle a cause or consequence of bacterial community dysbiosis or urinary symptoms? As sequencing costs continue to decline, studies such as that by Moustafa et al. [107] and Garretto et al. [99] are particularly powerful in capturing the dynamics between phages and their hosts.

Knowledge of the phage communities within the lower urinary tract and their role in urinary tract health is a vital first step in the development of new strategies to treat urinary symptoms and infections. Phage therapy has the potential to combat antibiotic resistant

bacterial infections and other maladies, and anecdotal evidence of its success certainly warrants further investigation [147]. Phage/drug cocktails are promising as well; for instance, such a cocktail was recently used to clear a vascular graft *P. aeruginosa* infection [148]. Critical to effective and reliable phage therapy strategies, however, is the understanding of the extant beneficial microbiota. Phage therapies should ideally cause minimal to no disturbance of this community. In contrast to broad-spectrum antibiotics, phages can be directed very narrowly toward a specific bad player within the community. Given the observed novelty of many of the phages sequenced from urine and from the bladder [106,118], perhaps the genomes of the gate-keepers of urinary tract health have already been sequenced. Our understanding of the phage population of the urinary tract is in its infancy and future studies will likely open new areas of investigation.

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References

1. Huttenhower C et al. Structure, function and diversity of the healthy human microbiome. Nature 486, 207–214 (2012). [PubMed: 22699609]
2. Aagaard K et al. The Human Microbiome Project strategy for comprehensive sampling of the human microbiome and why it matters. The FASEB Journal 27, 1012–1022 (2013). [PubMed: 23165986]
3. Thomas-White K, Brady M, Wolfe AJ & Mueller ER The bladder is not sterile: History and current discoveries on the urinary microbiome. Curr Bladder Dysfunct Rep 11, 18–24 (2016). [PubMed: 27182288]
4. Fouts DE et al. Integrated next-generation sequencing of 16S rDNA and metaproteomics differentiate the healthy urine microbiome from asymptomatic bacteriuria in neuropathic bladder associated with spinal cord injury. J Transl Med 10, 174 (2012). [PubMed: 22929533]
5. Wolfe AJ et al. Evidence of uncultivated bacteria in the adult female bladder. J Clin Microbiol 50, 1376–1383 (2012). [PubMed: 22278835]
6. Brubaker L et al. Urinary bacteria in adult women with urgency urinary incontinence. Int Urogynecol J 25, 1179–1184 (2014). [PubMed: 24515544]
7. Hilt EE et al. Urine is not sterile: Use of enhanced urine culture techniques to detect resident bacterial flora in the adult female bladder. J Clin Microbiol 52, 871–876 (2014). [PubMed: 24371246]
8. Pearce MM et al. The female urinary microbiome: A comparison of women with and without urgency urinary incontinence. mBio 5, e01283–14-e01283–14 (2014).
9. Pearce MM et al. The female urinary microbiome in urgency urinary incontinence. Am J Obstet Gynecol 213, 347.e1–347.e11 (2015).
10. Thomas-White K, Fok C, Mueller ER, Wolfe AJ & Brubaker L Pre-operative urinary microbiome reveals post-operative urinary tract infection risk. Neurourol Urodynam 34, S21–S22 (2015).
11. Karstens L et al. Does the urinary microbiome play a role in urgency urinary incontinence and its severity? Front Cell Infect Microbiol 6, 78 (2016). [PubMed: 27512653]
12. Ackerman AL & Underhill DM The mycobiome of the human urinary tract: potential roles for fungi in urology. Ann Transl Med 5, 31–31 (2017). [PubMed: 28217696]
13. Whiteside SA, Razvi H, Dave S, Reid G & Burton JP The microbiome of the urinary tract—a role beyond infection. Nat Rev Urol 12, 81–90 (2015). [PubMed: 25600098]

14. Fok CS et al. Day of surgery urine cultures identify urogynecologic patients at increased risk for postoperative urinary tract infection. J Urol 189, 1721–1724 (2013). [PubMed: 23219547]
15. Nienhouse V et al. Interplay between bladder microbiota and urinary antimicrobial peptides: Mechanisms for human urinary tract infection risk and symptom severity. PLoS ONE 9, e114185 (2014).
16. Thomas-White KJ et al. Incontinence medication response relates to the female urinary microbiota. Int Urogynecol J 27, 723–733 (2016). [PubMed: 26423260]
17. Brubaker L & Wolfe AJ Microbiota in 2016: Associating infection and incontinence with the female urinary microbiota. Nat Rev Urol 14, 72–74 (2017). [PubMed: 28050013]
18. Mueller ER, Wolfe AJ & Brubaker L Female urinary microbiota. Curr Opin Urol 27, 282–286 (2017). [PubMed: 28234750]
19. Thomas-White K Culturing of female bladder bacteria reveals an interconnected urogenital microbiome. Nat Commun 9, 8350 (2018).
20. Wylie KM et al. Metagenomic analysis of double-stranded DNA viruses in healthy adults. BMC Biol 12, 71 (2014). [PubMed: 25212266]
21. Lloyd-Price J, Abu-Ali G & Huttenhower C The healthy human microbiome. Genome Med 8, 51 (2016). [PubMed: 27122046]
22. Minot S et al. Rapid evolution of the human gut virome. Proc Natl Acad Sci U S A 110, 12450–12455 (2013). [PubMed: 23836644]
23. Minot S et al. The human gut virome: Inter-individual variation and dynamic response to diet. Genome Res 21, 1616–1625 (2011). [PubMed: 21880779]
24. Norman JM et al. Disease-specific alterations in the enteric virome in inflammatory bowel disease. Cell 160, 447–460 (2015). [PubMed: 25619688]
25. Lim ES et al. Early life dynamics of the human gut virome and bacterial microbiome in infants. Nat Med 21, 1228–1234 (2015). [PubMed: 26366711]
26. Ogilvie LA & Jones BV The human gut virome: a multifaceted majority. Front Microbiol 6, (2015).
27. Manrique P et al. Healthy human gut phageome. Proc Natl Acad Sci U S A 113, 10400–10405 (2016). [PubMed: 27573828]
28. Manrique P, Dills M & Young M The human gut phage community and its implications for health and disease. Viruses 9, 141 (2017).
29. Wagner J et al. Bacteriophages in gut samples from pediatric Crohn's Disease patients: Metagenomic analysis using 454 Pyrosequencing. Inflamm Bowel Dis 19, 1598–1608 (2013). [PubMed: 23749273]
30. Ma Y, You X, Mai G, Tokuyasu T & Liu C A human gut phage catalog correlates the gut phageome with type 2 diabetes. Microbiome 6, (2018).
31. Foulongne V et al. Human skin microbiota: high diversity of DNA viruses identified on the human skin by high throughput sequencing. PLoS ONE 7, e38499 (2012).
32. Pride DT et al. Evidence of a robust resident bacteriophage population revealed through analysis of the human salivary virome. ISME J 6, 915–926 (2012). [PubMed: 22158393]
33. Ly M et al. Altered oral viral ecology in association with periodontal disease. MBio 5, e01133–01114 (2014).
34. Hannigan GD et al. The human skin double-stranded DNA virome: topographical and temporal diversity, genetic enrichment, and dynamic associations with the host microbiome. MBio 6, e01578–01515 (2015).
35. Hannigan GD et al. Evolutionary and functional implications of hypervariable loci within the skin virome. PeerJ 5, e2959 (2017). [PubMed: 28194314]
36. Pérez-Brocal V & Moya A The analysis of the oral DNA virome reveals which viruses are widespread and rare among healthy young adults in Valencia (Spain). PLoS ONE 13, e0191867 (2018).
37. Chibani-Chennoufi S, Bruttin A, Dillmann M-L & Brussow H Phage-Host Interaction: An Ecological Perspective. J Bacteriol 186, 3677–3686 (2004). [PubMed: 15175280]

38. Breitbart M, Bonnain C, Malki K & Sawaya NA Phage puppet masters of the marine microbial realm. Nat Microbiol 3, 754–766 (2018). [PubMed: 29867096]
39. Williamson KE, Radosevich M & Wommack KE Abundance and diversity of viruses in six Delaware soils. Appl Environ Microbiol 71, 3119–3125 (2005). [PubMed: 15933010]
40. Williamson KE, Fuhrmann JJ, Wommack KE & Radosevich M Viruses in soil ecosystems: An unknown quantity within an unexplored territory. Annu Rev Virol 4, 201–219 (2017). [PubMed: 28961409]
41. Bruder K et al. Freshwater Metaviromics and Bacteriophages: A Current Assessment of the State of the Art in Relation to Bioinformatic Challenges. Evol Bioinform Online 12, 25–33 (2016). [PubMed: 27375355]
42. Prestel E, Regeard C, Salamitou S, Neveu J & Dubow MS The bacteria and bacteriophages from a Mesquite Flats site of the Death Valley desert. Antonie Van Leeuwenhoek 103, 1329–1341 (2013). [PubMed: 23559041]
43. Luhtanen A-M et al. Isolation and characterization of phage–host systems from the Baltic Sea ice. Extremophiles 18, 121–130 (2014). [PubMed: 24297705]
44. Nigro OD et al. Viruses in the oceanic basement. mBio 8, e02129–16 (2017).
45. Koskella B & Parr N The evolution of bacterial resistance against bacteriophages in the horse chestnut phyllosphere is general across both space and time. Philos Trans R Soc Lond B Biol Sci 370, 20140297 (2015).
46. Pramono AK et al. Discovery and complete genome sequence of a bacteriophage from an obligate intracellular symbiont of a cellulolytic protist in the termite gut. Microbes Environ 32, 112–117 (2017). [PubMed: 28321010]
47. Moreno PS et al. Characterisation of the canine faecal virome in healthy dogs and dogs with acute diarrhoea using shotgun metagenomics. PLoS ONE 12, e0178433 (2017).
48. Barr JJ A bacteriophages journey through the human body. Immunol Rev 279, 106–122 (2017). [PubMed: 28856733]
49. Navarro F & Muniesa M Phages in the human body. Front Microbiol 8, (2017).
50. Górski A et al. Bacteriophage translocation. FEMS Immunol Med Microbiol 46, 313–319 (2006). [PubMed: 16553803]
51. Nguyen S et al. Bacteriophage transcytosis provides a mechanism to cross epithelial cell layers. mBio 8, e01874–17 (2017).
52. Koskella B & Meaden S Understanding bacteriophage specificity in natural microbial communities. Viruses 5, 806–823 (2013). [PubMed: 23478639]
53. Young R Phage lysis: Three steps, three choices, one outcome. J Microbiol 52, 243–258 (2014). [PubMed: 24585055]
54. Little J Lysogeny, Prophage Induction, and Lysogenic Conversion. in Phages Their Role in Bacterial Pathogenesis and Biotechnology (eds. Waldor M, Friedman D & Adhya S) 37–54 (ASM Press, 2005).
55. Abedon ST Bacteriophage ecology: population growth, evolution, and impact of bacterial viruses. (Cambridge University Press, 2008).
56. Erez Z et al. Communication between viruses guides lysis-lysogeny decisions. Nature 541, 488–493 (2017). [PubMed: 28099413]
57. Calendar R The bacteriophages. (Oxford University Press, 2006).
58. Hobbs Z & Abedon ST Diversity of phage infection types and associated terminology: the problem with ‘Lytic or lysogenic’. FEMS Microbiol Lett 363, (2016).
59. Fuhrman JA Marine viruses and their biogeochemical and ecological effects. Nature 399, 541–548 (1999). [PubMed: 10376593]
60. Suttle CA Viruses in the sea. Nature 437, 356–361 (2005). [PubMed: 16163346]
61. Clokie MRJ, Millard AD, Letarov AV & Heaphy S Phages in nature. Bacteriophage 1, 31–45 (2011). [PubMed: 21687533]
62. Buckling A & Rainey PB Antagonistic coevolution between a bacterium and a bacteriophage. Proc Biol Sci 269, 931–936 (2002). [PubMed: 12028776]

63. Rodriguez-Valera F et al. Explaining microbial population genomics through phage predation. Nat Rev Microbiol 7, 828–836 (2009). [PubMed: 19834481]
64. Koskella B & Brockhurst MA Bacteria-phage coevolution as a driver of ecological and evolutionary processes in microbial communities. FEMS Microbiol Rev 38, 916–931 (2014). [PubMed: 24617569]
65. Tellier A, Moreno-Gámez S & Stephan W Speed of adaptation and genomic footprints of host-parasite coevolution under arms race and trench warfare dynamics. Evolution 68, 2211–2224 (2014). [PubMed: 24749791]
66. Braga LPP, Soucy SM, Amgarten DE, da Silva AM & Setubal JC Bacterial diversification in the light of the interactions with phages: The Genetic Symbionts and Their Role in Ecological Speciation. Front Ecol Evol 6, (2018).
67. Scanlan PD Bacteria–Bacteriophage Coevolution in the Human Gut: Implications for Microbial Diversity and Functionality. Trends Microbiol 25, 614–623 (2017). [PubMed: 28342597]
68. Hosseinidoust Z, van de Ven TGM & Tufenkji N Evolution of Pseudomonas aeruginosa virulence as a result of phage predation. Appl Environ Microbiol 79, 6110–6116 (2013). [PubMed: 23892756]
69. Wendling CC et al. Tripartite species interaction: eukaryotic hosts suffer more from phage susceptible than from phage resistant bacteria. BMC Evol Biol 17, 98 (2017). [PubMed: 28399796]
70. Wagner PL & Waldor MK Bacteriophage control of bacterial virulence. Infect Immun 70, 3985–3993 (2002). [PubMed: 12117903]
71. Casas V & Maloy S Role of bacteriophage-encoded exotoxins in the evolution of bacterial pathogens. Future Microbiol 6, 1461–1473 (2011). [PubMed: 22122442]
72. Starr M et al. Hemolytic-uremic syndrome following urinary tract infection with enterohemorrhagic Escherichia coli: case report and review. Clin Infect Dis 27, 310–315 (1998). [PubMed: 9709881]
73. Gadea M et al. Two cases of urinary tract infection caused by Shiga toxin-producing Escherichia coli O157:H7 strains. Rev Argent Microbiol 44, 94–96 (2012). [PubMed: 22997767]
74. Toval F et al. Characterization of urinary tract infection-associated shiga toxin-producing Escherichia coli. Infect Immun 82, 4631–4642 (2014). [PubMed: 25156739]
75. Harrison E & Brockhurst MA Ecological and evolutionary benefits of temperate phage: What does or doesn't kill you makes you stronger. BioEssays 39, 1700112 (2017).
76. Touchon M, Moura de Sousa JA & Rocha EP Embracing the enemy: the diversification of microbial gene repertoires by phage-mediated horizontal gene transfer. Curr Opin Microbiol 38, 66–73 (2017). [PubMed: 28527384]
77. Drexler H Transduction by bacteriophage T1. Proc Natl Acad Sci USA 66, 1083–1088 (1970). [PubMed: 4920089]
78. Modi SR, Lee HH, Spina CS & Collins JJ Antibiotic treatment expands the resistance reservoir and ecological network of the phage metagenome. Nature 499, 219–222 (2013). [PubMed: 23748443]
79. Abeles SR, Ly M, Santiago-Rodriguez TM & Pride DT Effects of Long Term Antibiotic Therapy on Human Oral and Fecal Viromes. PLoS ONE 10, e0134941 (2015).
80. Enault F et al. Phages rarely encode antibiotic resistance genes: a cautionary tale for virome analyses. ISME J 11, 237–247 (2017). [PubMed: 27326545]
81. Lood R, Ertürk G & Mattiasson B Revisiting antibiotic resistance spreading in wastewater treatment plants-Bacteriophages as a much neglected potential transmission vehicle. Front Microbiol 8, 2298 (2017). [PubMed: 29209304]
82. Keen EC et al. Novel "Superspreader" bacteriophages promote horizontal gene transfer by transformation. mBio 8, e02115–16 (2017).
83. Hatfull GF Dark matter of the biosphere: The amazing world of bacteriophage diversity. J Virol 89, 8107–8110 (2015). [PubMed: 26018169]
84. Roux S, Hallam SJ, Woyke T & Sullivan MB Viral dark matter and virus-host interactions resolved from publicly available microbial genomes. Elife 4, (2015).

85. Wang J, Gao Y & Zhao F Phage-bacteria interaction network in human oral microbiome: Human oral virome. Environ Microbiol 18, 2143–2158 (2016). [PubMed: 26036920]
86. Shapiro JW & Putonti C Gene Co-occurrence Networks Reflect Bacteriophage Ecology and Evolution. mBio 9, e01870–17 (2018).
87. Hayes S, Mahony J, Nauta A & van Sinderen D Metagenomic approaches to assess bacteriophages in various environmental niches. Viruses 9, (2017).
88. Kristensen DM et al. Orthologous gene clusters and taxon signature genes for viruses of prokaryotes. J Bacteriol 195, 941–950 (2013). [PubMed: 23222723]
89. Adriaenssens EM & Cowan DA Using signature genes as tools to assess environmental viral ecology and diversity. Appl Environ Microbiol 80, 4470–4480 (2014). [PubMed: 24837394]
90. Paez-Espino D et al. IMG/VR: a database of cultured and uncultured DNA viruses and retroviruses. Nucleic Acids Res 45, D457–D465 (2017). [PubMed: 27799466]
91. Paez-Espino D et al. Uncovering Earth's virome. Nature 536, 425–430 (2016). [PubMed: 27533034]
92. Echavarria M, Forman M, Ticehurst J, Dumler JS & Charache P PCR method for detection of adenovirus in urine of healthy and human immunodeficiency virus-infected individuals. J Clin Microbiol 36, 3323–3326 (1998). [PubMed: 9774586]
93. Lion T Adenovirus infections in immunocompetent and immunocompromised patients. Clin Microbiol Rev 27, 441–462 (2014). [PubMed: 24982316]
94. Tan SK, Relman DA & Pinsky BA The human virome: Implications for clinical practice in transplantation medicine. J Clin Microbiol 55, 2884–2893 (2017). [PubMed: 28724557]
95. Rani A et al. A diverse virome in kidney transplant patients contains multiple viral subtypes with distinct polymorphisms. Sci Rep 6, (2016).
96. Chang H et al. High incidence of JC viruria in JC-seropositive older individuals. J Neurovirol 8, 447–451 (2002). [PubMed: 12402171]
97. Hirsch HH, Kardas P, Kranz D & Leboeuf C The human JC polyomavirus (JCPyV): virological background and clinical implications. APMIS 121, 685–727 (2013). [PubMed: 23781977]
98. Rinaldo CH, Tylden GD & Sharma BN The human polyomavirus BK (BKPyV): virological background and clinical implications. APMIS 121, 728–745 (2013). [PubMed: 23782063]
99. Garretto A, Thomas-White K, Wolfe AJ & Putonti C Detecting viral genomes in the female urinary microbiome. J Gen Virol 99, 1141–1146 (2018). [PubMed: 29889019]
100. Thannesberger J et al. Viruses comprise an extensive pool of mobile genetic elements in eukaryote cell cultures and human clinical samples. The FASEB J 31, 1987–2000 (2017). [PubMed: 28179422]
101. Tshomo U et al. Evaluation of the performance of Human Papillomavirus testing in paired urine and clinician-collected cervical samples among women aged over 30 years in Bhutan. Virol J 14, 74 (2017). [PubMed: 28390433]
102. Iwasawa A et al. Presence of human papillomavirus 6/11 DNA in condyloma acuminatum of the urinary bladder. Urol Int 48, 235–238 (1992). [PubMed: 1316664]
103. Karim RZ, Rose BR, Brammah S & Scolyer RA Condylomata acuminata of the urinary bladder with HPV 11. Pathology 37, 176–178 (2005). [PubMed: 16028850]
104. Chrisofos M, Skolarikos A, Lazaris A, Bogris S & Deliveliotis C HPV 16/18-associated condyloma acuminatum of the urinary bladder: first international report and review of literature. Int J STD AIDS 15, 836–838 (2004). [PubMed: 15601491]
105. Murray AJ, Bivalacqua TJ & Sopko NA Innumerable Condyloma Acuminatum tumors of the bladder. Urol Case Rep 12, 76–77 (2017). [PubMed: 28377892]
106. Santiago-Rodriguez TM, Ly M, Bonilla N & Pride DT The human urine virome in association with urinary tract infections. Front Microbiol 6, 14 (2015). [PubMed: 25667584]
107. Moustafa A et al. Microbial metagenome of urinary tract infection. Sci Rep 8, (2018).
108. d'Herelle F Sur un microbe invisible antagoniste des bacilles dysenteriques. Comptes rendus Acad Sciences 165, 373–375 (1917).
109. Brown-Jaque M, Muniesa M & Navarro F Bacteriophages in clinical samples can interfere with microbiological diagnostic tools. Sci Rep 6, (2016).

110. Jalil MB, Al-Hmudi HA, Al-Alsaad LA & Abdul-Hussein ZR Isolation and characterization of bacteriophages against multiple drug resistant Pseudomonas aeruginosa with using the bacteriophage as a therpy in the mice model. International Journal of Development Research 7, 11519 (2017).
111. Dallas SD & Kingsbery L Bacteriophage plaques on primary isolation media of a urine culture growing Escherichia coli. Clin Microbiol Newsl 19, 53–56 (1997).
112. Malki K et al. Seven Bacteriophages Isolated from the Female Urinary Microbiota. Genome Announc 4, (2016).
113. Smith R, O'Hara M, Hobman JL & Millard AD Draft genome sequences of 14 Escherichia coli phages isolated from cattle slurry. Genome Announc 3, e01364–15 (2015).
114. Putonti C, Garretto A, Shapiro JW & Wolfe AJ The role of bacterial viruses in the female urinary microbiome. Female Pelvic Med Reconstr Surg 23, S39–S40 (2017).
115. Kim M-S & Bae J-W Lysogeny is prevalent and widely distributed in the murine gut microbiota. ISME J 12, 1127–1141 (2018). [PubMed: 29416123]
116. Price TK et al. Genome sequences and annotation of two urinary isolates of E. coli. Stand Genomic Sci 11, 79 (2016). [PubMed: 27777649]
117. Malki K et al. Genomes of Gardnerella Strains Reveal an Abundance of Prophages within the Bladder Microbiome. PLoS ONE 11, e0166757 (2016).
118. Miller-Ensminger T et al. Bacteriophages of the urinary microbiome. J Bacteriol 200, e00738–17 (2018). [PubMed: 29378882]
119. Khasriya R et al. Spectrum of bacterial colonization associated with urothelial cells from patients with chronic lower urinary tract symptoms. J Clinl Microbiol 51, 2054–2062 (2013).
120. Price TK et al. The clinical urine culture: Enhanced techniques improve detection of clinically relevant microorganisms. J Clin Microbiol 54, 1216–1222 (2016). [PubMed: 26962083]
121. Bao Y et al. Questions and challenges associated with studying the microbiome of the urinary tract. Ann Transl Med 5, 33–33 (2017). [PubMed: 28217698]
122. Yilmaz S, Allgaier M & Hugenholtz P Multiple displacement amplification compromises quantitative analysis of metagenomes. Nat Methods 7, 943–944 (2010). [PubMed: 21116242]
123. Lewis DA et al. The human urinary microbiome; bacterial DNA in voided urine of asymptomatic adults. Front Cell Infect Microbiol 3, (2013).
124. Gangping L et al. Diversity of duodenal and rectal microbiota in biopsy tissues and luminal contents in healthy volunteers. J Microbiol Biotechnol 25, 1136–1145 (2015). [PubMed: 25737115]
125. Kim D et al. Optimizing methods and dodging pitfalls in microbiome research. Microbiome 5, 52 (2017). [PubMed: 28476139]
126. Panek M et al. Methodology challenges in studying human gut microbiota – effects of collection, storage, DNA extraction and next generation sequencing technologies. Sci Rep 8, 2045–2322 (2018). [PubMed: 29391556]
127. Brubaker L & Wolfe A The urinary microbiota: a paradigm shift for bladder disorders? Curr Opin Obstet Gynecol 28, 407–412 (2016). [PubMed: 27379439]
128. Holm A & Rune A Urine sampling techniques in symptomatic primary-care patients: a diagnostic accuracy review. BMC Fam Pract 17, 72 (2016). [PubMed: 27278078]
129. Łusiak-Szelachowska M, Weber-Dąbrowska B, Jończyk-Matysiak E, Wojciechowska R & Górski A Bacteriophages in the gastrointestinal tract and their implications. Gut Pathogens 9, (2017).
130. Barr JJ et al. Bacteriophage adhering to mucus provide a non-host-derived immunity. Proc Natl Acad Sci U S A 110, 10771–10776 (2013). [PubMed: 23690590]
131. Shan J et al. Bacteriophages are more virulent to bacteria with human cells than they are in bacterial culture; insights from HT-29 cells. Sci Rep 8, 5091 (2018). [PubMed: 29572482]
132. Dabrowska K et al. Antitumor activity of bacteriophages in murine experimental cancer models caused possibly by inhibition of beta3 integrin signaling pathway. Acta Virol 48, 241–248 (2004). [PubMed: 15745047]
133. Duerkop BA & Hooper LV Resident viruses and their interactions with the immune system. Nat Immunol 14, 654–659 (2013). [PubMed: 23778792]

134. Nieth A, Verseux C & Römer W A Question of attire: Dressing up bacteriophage therapy for the battle against antibiotic-resistant intracellular bacteria. Springer Sci Rev 3, 1–11 (2015).

135. Górski A et al. Phages and immunomodulation. Future Microbiol 12, 905–914 (2017). [PubMed: 28434234]

136. Dabrowska K et al. Immunogenicity studies of proteins forming the T4 phage head surface. J Virol 88, 12551–12557 (2014). [PubMed: 25142581]

137. Duerkop BA, Clements CV, Rollins D, Rodrigues JLM & Hooper LV A composite bacteriophage alters colonization by an intestinal commensal bacterium. Proc Natl Acad Sci U S A 109, 17621–17626 (2012). [PubMed: 23045666]

138. Gama JA et al. Temperate bacterial viruses as double-edged swords in bacterial warfare. PLoS ONE 8, e59043 (2013).

139. Lin DM, Koskella B & Lin HC Phage therapy: An alternative to antibiotics in the age of multi-drug resistance. World J Gastrointest Pharmacol Ther 8, 162 (2017). [PubMed: 28828194]

140. Caldwell JA Bacteriophagy in urinary infections following the administration of the bacteriophage therapeutically. Arch Intern Med 41, 189 (1928).

141. Gill G & Young RF Therapeutic applications of phage biology: history, practice and recommendations In Emerging Trends in Antibacterial Discovery (eds Miller AA & Miller PF) 367–407 (Caister Academic Press, 2011).

142. Sybesma W et al. Bacteriophages as potential treatment for urinary tract infections. Front Microbiol 7, (2016).

143. Khawaldeh A et al. Bacteriophage therapy for refractory Pseudomonas aeruginosa urinary tract infection. J Med Microbiol 60, 1697–1700 (2011). [PubMed: 21737541]

144. Leitner L et al. Bacteriophages for treating urinary tract infections in patients undergoing transurethral resection of the prostate: a randomized, placebo-controlled, double-blind clinical trial. BMC Urology 17, (2017).

145. Siddiq DM & Darouiche RO New strategies to prevent catheter-associated urinary tract infections. Nat Rev Urol 9, 305–314 (2012). [PubMed: 22508462]

146. Letkiewicz S et al. The perspectives of the application of phage therapy in chronic bacterial prostatitis. FEMS Immunol Med Microbiol 60, 99–112 (2010). [PubMed: 20698884]

147. Abedon ST, Kuhl SJ, Blasdel BG & Kutter EM Phage treatment of human infections. Bacteriophage 1, 66–85 (2011). [PubMed: 22334863]

148. Chan BK et al. Phage treatment of an aortic graft infected with Pseudomonas aeruginosa. Evol Med Public Health 2018, 60–66 (2018). [PubMed: 29588855]

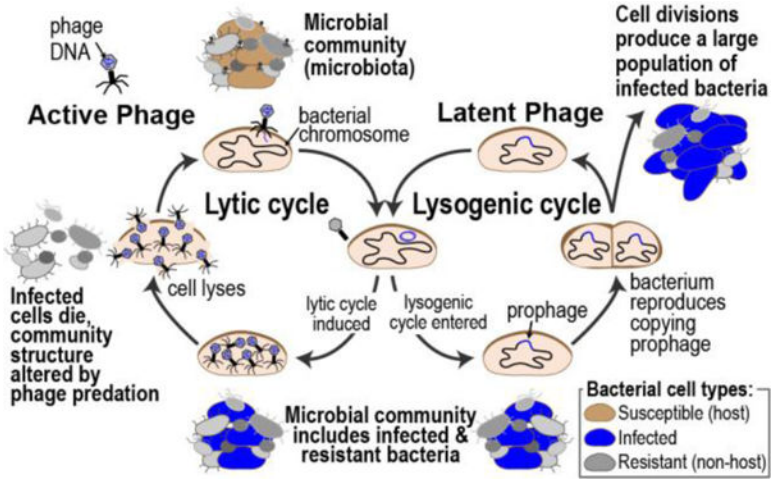

Fig. 1.

Lytic and lysogenic cycles of phages and their impact on microbiota

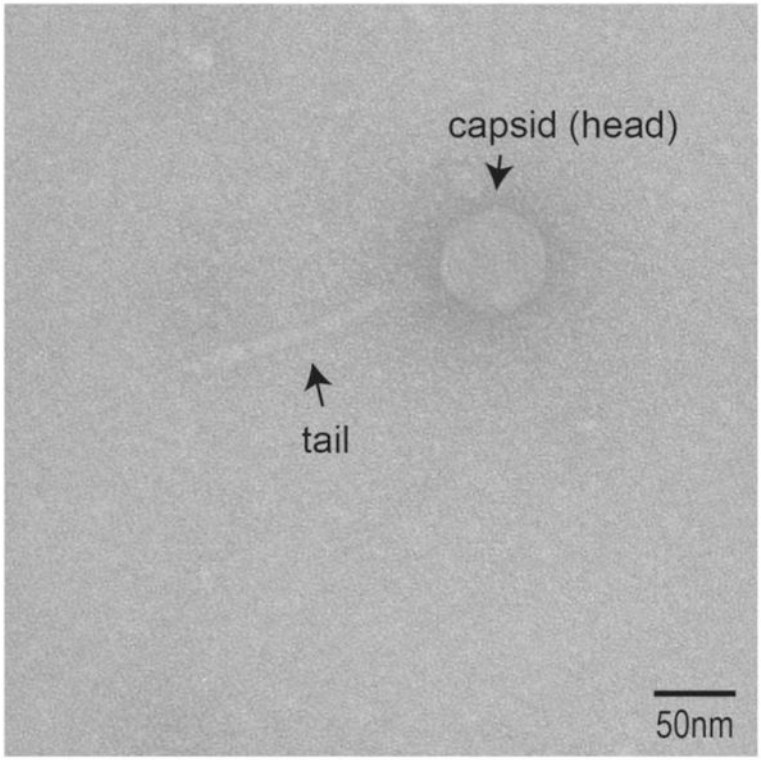

Fig. 2.
Bacteriophage Greed, isolated from catheterized urine microbiome sample.

Table 1.

Current number of viral sequences from virome studies of HMP anatomical sites (as of 4/2018). Clusters corresponds to genetically distinct groups. [Data retrieved from the IMG/VR system [90].]

	Airway	GI Tract	Oral	Skin	Urogenital tract/ vagina
Total # of Metagenomic Viral Contigs	268	29107	48904	2461	422
Unique Viral Clusters	41	3465	5246	200	67
Total # of Genomes	107	510	886	491	101