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Review Article

# How Near in Reality for Phage-Therapy as an Alternative to Antibiotics

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## Abstract

One of the major challenge in modern medicine is increasing the development of antibiotic resistance towards several antimicrobial agents by pathogenic bacteria. The evolution of multi-drug resistance bacteria leads to the search of antibiotic-free anti-infection strategies and has become the highest priority to modern medicine. One of such class of non-antibiotic and antibacterial agent to combat multi-drug resistance bacteria, that has high directional specificity towards bacteria is bacteriophages. Bacteriophages are most abundant organisms in all ecosystem. The fundamental understanding of phages and their relationship with hosts revitalizes the exploitation of phages systems to develop it as antibiotic alternatives. This article discusses the unparalleled insights on recent bacteriophage clinical trials results, strategies, advantages and their challenges.

**Keywords:** Antibiotics; Clinical Translation; Phage Therapy

## Introduction

The current biggest global health threat is antibiotic resistance. The indiscriminate use of antibiotics develops the generation of multidrug resistant and even pan-drug resistant pathogens [1]. A recent review report estimates an annual death of 10 million life by 2050 due to global rise of antimicrobial resistance with a total world GDP loss of US$ 100 trillion [2]. Further, the United Nations General Assembly on September 21, 2016, considered the antibiotic resistance as greatest and most urgent global risk [3]. A century old research and development on clinical application of phage undergone poorly designed, controlled trials in 1921 and arrival of golden area for antibiotics sharply collapse the phage therapy research [4,5]. Recent revived re-implementation of multidimensional, multidisciplinary strategy to combat antibiotic resistance through improved understanding of phage biology with advanced technologies.

Phage therapy involves the administration of bacteriophages or their derivatives to kill pathogenic bacterial infections in patients as an alternatives to antibiotics [5]. Phages are non-living biological entities consisting of relatively simple structure with DNA or RNA enclosed within a protein capsid. The bacteriophage that infects and hijacks the bacterial replicative system to produce their phage progeny and hydrolyze the peptidoglycan cell wall by their lytic cycle. The lysogenic phage's integrates the phage DNA into the bacterial chromosome allowing phage DNA to be propagated along the cell's DNA during replications as endogenous prophage. Recent new additions of phage lifecycles classification includes pseudolysogenic, chronic and cryptic lifecyles [6,7], apart from classical classification model (Figure 1). The therapeutic application relies on lytic phage cocktails preparation consist of multiple phages that are proven in-vitro efficacy against the target infective agent.

The clinical use of phage therapy as a antimicrobial agent was first made in 1919 at Hôpital des Enfants-Malades in Paris and successfully treated 4 paediatric cases [8]. Since then conventional phase therapy showed contradictory results and lack of proper standardized protocols for characterization and preparation [9]. Phage therapy has regained its presence in 2009 with phase-I placebo controlled trials in chronic leg ulcer and phase-I/II trial in chronic otitis with similar and improved outcome respectively [10, 11]. Till now, several clinical trials on phage therapy demonstrated to be safe and tolerable and had not reported any phage specific antibodies [12-14]. The PhagoBurn's randomised, controlled, double-blind phase I/II clinical trials results of 2019 against pseudomonas aeruginosa in infected burn wounds using cocktail of

natural lytic bacteriophages are not encouraging and are resistant to low phase doses [15]. AmpliPhi Biosciences Corporation is the world first company to receive the USFDA approval to conduct first intravenously administered bacteriophage based clinical trials for the treatment of skin and wound infections of methicillin-resistant (MRSA) strains. Several companies, organization and academics are now emerging to develop and to start pre-clinical trials with phage therapy and now in lag phase of development.

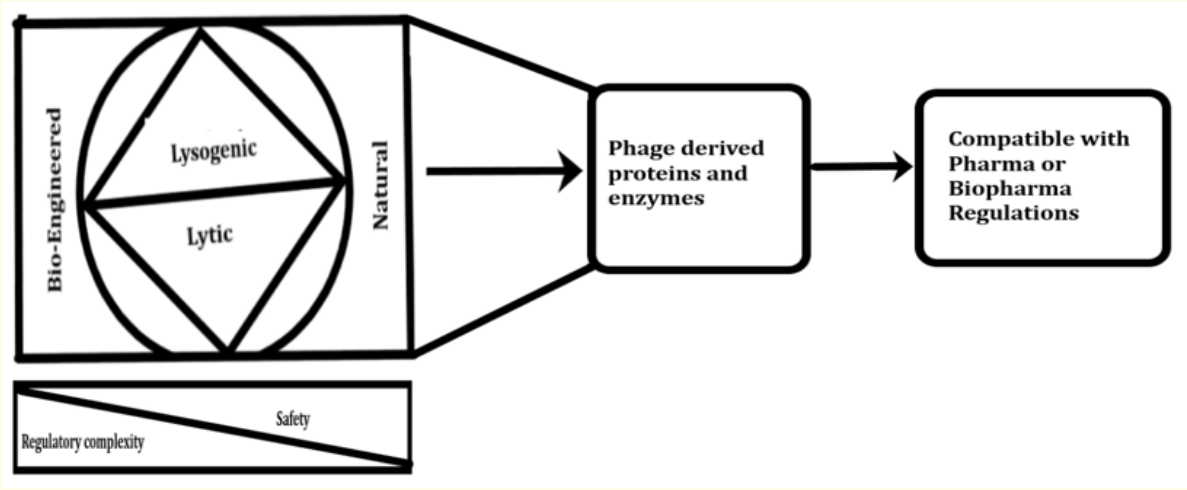


**Figure 1:** Classical classification of Bacteriophage. Lytic and lysogenic types forms the core main division of phages, within these exists natural and bio-engineered phages. The clinical and commercial translation of bio-engineered phages may encounter complex regulatory challenges.

Emergence of phage resistance to monophage therapy can overcome by administration of generic phage cocktails like Pyophage (PYO) and Intestiphage [16]. The safety and efficacy results of polyphage therapy are encouraging in preclinical trials [17,18]. Personalized phage cocktails enhances specificity towards sub-species level and decrease the probability of phage resistances and therapeutic failures [19]. But multiple phage production and preparation of phage cocktail formulation is quite challenging and cumbersome. In some cases, when used with the combination of antibiotics, the phages act as therapeutic catalyst to weaken the antibiotic resistant bacteria [20]. New dimension of utilizing the phage is through phage-derived proteins like Holins and endolysins. The sub-lethal concentration of Holin triggers the permeabilization of the inner cell membrane enabling to lysis [21,22]. Endolysin has natural cell wall lysing properties and Endolysin based therapy was in phase-I and Phase-II clinical trials [23,24]. Overall, the active clinical research is in progress to identify the suitable variety of broad spectrum of various phage therapy strategies and phage derived therapeutics.

## Challenges

1. Emergences of phage resistance by host bacteria. Single phage strain can effect only a single bacteria strain. The collection and development of the phage bank [25] of various strain and identifying the potent phage strain against the mutated bacterial strain helps to reduce and control bacteria resistance to new antibiotics and phages. Preventing the phage to develop resistance is a key area of active research. The precision matched personalized phage therapeutics is in nascent stage of development.
2. Detection of anti-phage antibodies or anti-phage neutralizing antibodies [26] and its clearances during repeat dose studies. On the other hand, there is no correlation on clinical outcome of phage therapy with anti-phage level [27].
3. Production of phage are associated with the high levels of Endotoxins. Howsoever, there are several strategies to control and minimize the Endotoxin limit in final formulation [28].
4. High specificity of phage therapy enhances narrow range or non-effective, even the small difference exists in sub-species of same bacteria.

5. No extensive acute and chronic toxicity studies.
6. No extensive bio-distribution studies.
7. Stability and shelf-life of lytic phage and factors effecting to lysogenic transmission of phage.
8. Enabling the pre-existing legal and regulatory frame work as a primitive regulatory establishment for clinical-scale production, testing and vigilance of phage therapy. Further developing the road-map to build the unified regulatory guidelines specific to phage-based clinical translation and commercialization.
9. Naturally occurring phage cannot be patented and rises the concerns on management of intellectual property rights.
10. Significant clinical evidence about its efficacy on large population not yet demonstrated.

### Advantage of phage based therapeutics

1. Specificity towards target bacteria strain and does not harm natural microflora.
2. Bacteriophage does not effects on human cells and are safe to use for clinical translation studies.
3. Cost-effective production process with amicable for large-scale production.
4. Non-engineered phage are the natural component of environment and no risk of environmental hazards and low environmental impact.
5. No risk of antibiotic allergies.
6. Highly stable under harsh environmental conditions reduces cold-chain management studies as well as pre-infusion stability studies.
7. Bacteria killing process by bacteriophages facilitates the auto-dosing capabilities.
8. Can be a potent adjuvant, if used as a phage DNA vaccines.
9. Suitable for most route of administration and formulation versatility. It can also be used with combinations of antibiotics. In addition, Bacteriophage therapy is compatible with cell and tissue based therapies as advanced wound healing regenerative products, where antibiotics hamper therapeutic cell activation and efficacy.
10. Its efficacy is through active phage amplification and the possibility of development of single dose therapy cannot be ruled out.

### Future direction

Bio-engineered phages or genetically modified phage can increase the efficacy like stimulating strong lytic activity [29], conjugating polyethylene glycol increases the bio-availability and improves the pharmokinetics parameters [30]. The delivering antibiotic directly to bacteria cells by attaching antibiotic molecule to lytic phage and phage mediated lethal gene delivery [31,32]. The lysogenic bio-engineered phage are untapped promising area to be developed in conjugation with vaccinology. The antigen is cloned into the phage capsid proteins allowing to be readily present to antigen presenting cells of innate and adoptive immune system [33]. Phage research is quickly shifting towards ever expanding field of drug discovery, biocontrol and agriculture.

## Conclusions

Phage research and its application is still in its infancy, in spite of rapid basic and translational studies. Creation of natural phage bank at national level is first step of development to fasten the phage research program. Many of the naturally occurring phages are not completely characterized and its full potential have not been fully explored. Clear evidence of efficacy of bacteriophage therapy in large population through clinical trials needs to be determined as per standards of evidence-based medicine.

## Conflict of Interest

The author have no conflict of interest.

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