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PHAGE THERAPY IN CHILDREN WITH ANTIBIOTIC-RESISTANT INFECTIONS: A COMPREHENSIVE REVIEW

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ABSTRACT

Introduction: This systematic review explores the use of bacteriophage (phage) therapy in treating antibiotic-resistant infections in pediatric patients. With increasing global antibiotic resistance, especially in vulnerable populations such as children, phage therapy emerges as a targeted and adaptable alternative. The review synthesizes findings from clinical case reports, retrospective studies, and early-phase trials, focusing on the efficacy, safety, and application of personalized phage cocktails. Although further standardization is needed, the evidence supports phage therapy as a promising non-antibiotic strategy for managing resistant infections in children.

Aim of the Study: The aim of the study is to assess the clinical potential of phage therapy in pediatric patients suffering from infections caused by multidrug-resistant (MDR) or extensively drug-resistant (XDR) bacteria. The review focuses on evaluating treatment outcomes, safety considerations, and the logistical framework required for its implementation in hospital settings.

Materials and Methods: A systematic literature search was conducted in databases including PubMed and ScienceDirect using keywords such as "phage therapy", "bacteriophages", "antibiotic resistance", "multidrug-resistant infections", and "pediatric infectious diseases". Selected studies included clinical trials, case reports, and expert reviews focusing on children treated with bacteriophages between 2015 and 2025.

Summary: This review highlights phage therapy as a viable adjunct or alternative to antibiotics in treating drug-resistant infections in children. Clinical outcomes suggest good tolerability and success in personalized treatments, particularly where antibiotics have failed. Although regulatory, production, and access barriers exist, the growing clinical experience and innovation in phage formulation suggest strong future potential in pediatric infectious disease care.

KEYWORDS

Phage Therapy, Antibiotic Resistance, Pediatric Infections, Multidrug-Resistant Bacteria, Personalized Medicine, Bacteriophages

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Introduction

Antibiotic resistance has become a critical global health threat, with increasing reports of bacterial infections that fail to respond to standard antimicrobial therapies. Children in particular are vulnerable to multidrug-resistant infections, which often results in prolonged hospitalizations or limited treatment options. Their organisms have not fully developed immune mechanisms and by using lots of different antibiotics it only makes them more susceptible for next infections. To break this vicious circle bacteriophages come in handy. They were discovered in the early 20th century, but recently they have re-emerged as a promising way to treat bacterial infections [1].

Phage therapy is usable in pediatrics for several reasons. Firstly, children with chronic conditions (such as cystic fibrosis or immunodeficiencies) often suffer from recurrent resistant infections that could be targeted by phages when antibiotics fail. Secondly, phage therapy's high specificity means it can selectively target pathogens without disturbing the child's developing microbiome, potentially reducing side effects, like for example antibiotic-associated diarrhea. Finally, case reports suggest that phage therapy can be administered safely even in very ill children.

The objective of this review is to provide a comprehensive overview of phage therapy in children with antibiotic-resistant infections. We begin by explaining the mechanism of phages action and compare phage therapy to antibiotic treatment. Then we will proceed to review the current state of clinical research and applications of pediatric phage therapy in cases and studies from roughly 2015–2025. Next, we discuss the reported safety, efficacy, and tolerability of this therapy in children based on clinical case reports and trials.

We address practical challenges in implementing phage therapy – including regulatory hurdles, production and formulation issues, and the potential for bacterial resistance to phages. Finally, we conclude with a summary of key findings and suggestions for future research to advance phage therapy as a viable pediatric treatment modality.

Mechanism of Bacteriophage Action and Comparison to Antibiotics

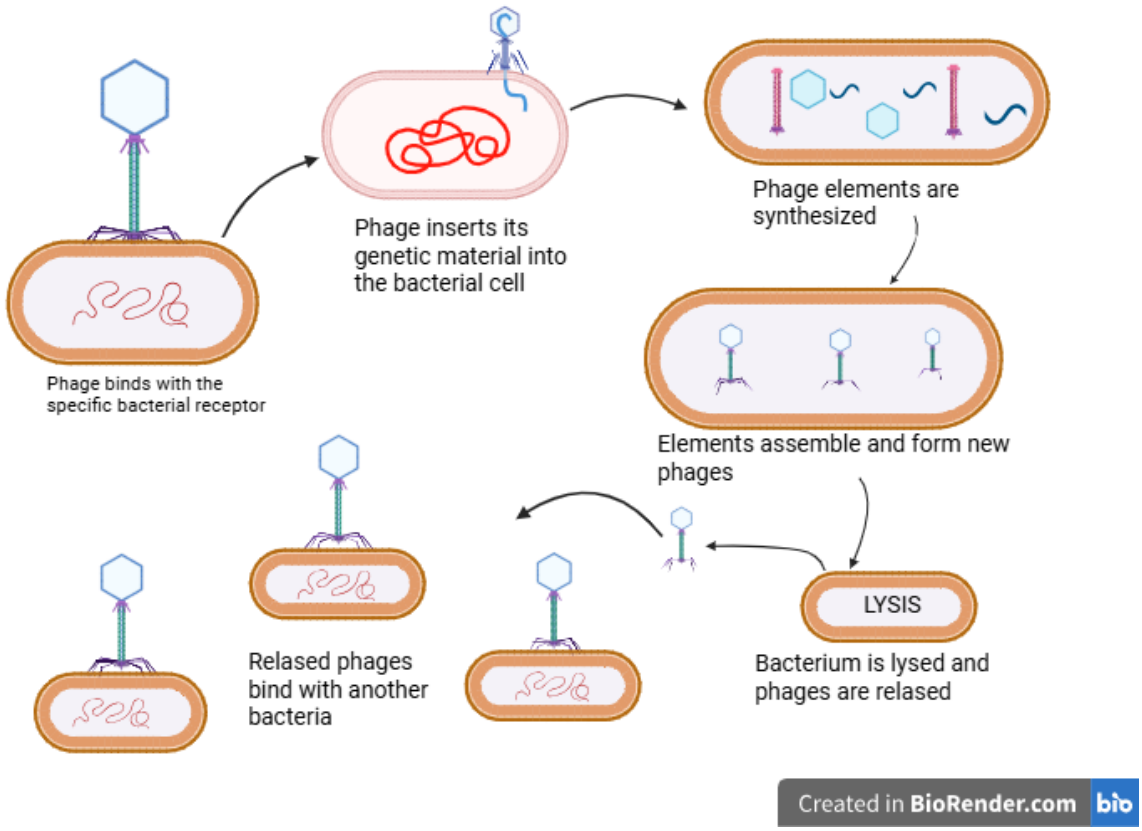

Fig. 1. *The lytic life cycle of a bacteriophage.*

Phages are viruses that are meant to infect only specific bacteria. It is possible due to receptors present on the bacterial wall. Phages identify them and bind with the bacterium. It allows inserting its genetic material into the bacterial cell. The genetic material of the phage uses the bacterial transcriptional and translational apparatus to synthesise its own proteins and replicate the genome, making elements needed to form a new phage. Then components are assembled inside the bacterial cell. Newly formed phages produce lytic enzymes which induce bacterial lysis. Phages are released and they infect other bacteria nearby. This cycle repeats as long as bacteria are present, allowing phages to amplify at the site of infection – what is described as "auto-dosing. In essence, each phage acts as a self-replicating antimicrobial agent that increases in number where its bacterial host is found, In contrast to antibiotics whose concentration will only decline without repeated dosing [1].

Broad-spectrum antibiotics affect a wide range of bacterial species - also our natural bacterial flora. Whereas phages are usually limited to a single bacteria species or even specific strains. In pediatric patients, preserving the microbiome is particularly beneficial to avoid antibiotic-associated infections - for example: *Clostridioides difficile* colitis or secondary yeast infections. [1]

Phage Therapy vs. Traditional Antibiotics: Phage therapy offers several theoretical and practical advantages over conventional antibiotics, especially in the context of antibiotic-resistant infections. A major advantage of phages is that they have unique mechanisms that do not overlap with those of antibiotics. Thus, bacteria resistant to multiple antibiotics may still be susceptible to lytic phages. There is no cross-resistance between antibiotics and phages, for example, mechanisms like antibiotic efflux pumps or target mutations do not help a bacterium evade phage infection [1]. In fact, phages can be effective against bacteria that are pan-resistant to all available antibiotics [1] Moreover, some phage-resistant bacterial mutants have reduced fitness

or virulence because of the mutations (such as loss of a surface receptor used by the phage) can also impede the bacterium's pathogenic mechanisms [1]. Another benefit of phages is their ability to penetrate and disrupt biofilms. Many chronic pediatric infections (such as cystic fibrosis lung infections or chronic otitis) involve bacteria growing in biofilms, which are notoriously resistant to antibiotics. Lytic phages, however, have been shown to digest the extracellular matrix of biofilms and propagate within these structures, potentially succeeding where antibiotics alone often fail [2].

Pharmacokinetically, phages differ from antibiotics in significant ways. Phages are large entities (virus particles) and may have limited diffusion in tissue or difficulty crossing certain barriers, whereas small-molecule antibiotics can often penetrate better. On the other hand, as noted, phages amplify at the infection focus, whereas antibiotics dilute over time [1]. This means an initial low dose of phage can theoretically increase to high local concentrations if the bacterial burden is high, something antibiotics cannot do (antibiotics must be continuously delivered or reach high systemic levels) [1]. The self-limiting nature of phages is also noteworthy: once the target bacteria are eliminated, phages have no hosts to infect and their numbers will decline, which may reduce long-term exposure and side effects [1]. In terms of toxicity, phages are composed of nucleic acids and proteins and are not known to have direct toxic effects on human cells;[1]. Adverse effects from phage therapy, when observed, usually stem from immune system reactions (e.g., inflammatory responses to rapid bacterial lysis or to bacterial debris like endotoxins released during lysis) rather than toxicity of the phage itself [1]. This contrasts with certain antibiotics that can have direct toxic side effects (for instance, aminoglycosides can damage kidneys and hearing). Indeed, in many compassionate-use phage treatments, patients have tolerated high doses and prolonged courses of phages without serious adverse effects [3].

However, there are also challenges and limitations to phage therapy as compared to antibiotics. The narrow host range means that a phage (or phage cocktail) must be carefully selected to match the specific pathogen causing a child's infection; if misidentified, the therapy will fail, whereas a broad-spectrum antibiotic might still have some effect even if the exact pathogen was unknown. Additionally, the need to develop or obtain a phage for each pathogen can delay treatment initiation, unlike antibiotics, which are often immediately available, phages may need to be isolated and purified anew for rare bacteria. In urgent pediatric infections, the time factor is critical. Another concern is the potential for the patient's immune system to recognize and neutralize the phages (producing anti-phage antibodies), especially on repeated or long-term administration. Such antibodies can clear phages from circulation and reduce efficacy [3]. By contrast, while antibiotics can trigger allergic reactions, they generally are not neutralized by immune antibodies in a way that stops their antimicrobial action. Finally, whereas antibiotics are governed by well-established dosing, pharmacodynamic, and regulatory frameworks, phage therapy is still navigating these aspects (phages have unusual pharmacokinetics and currently lack standardized regulatory approval in most countries, as discussed later) [3]

In summary, bacteriophages combat bacteria through a lytic lifecycle that is fundamentally different from antibiotic action, offering bactericidal activity even against drug-resistant pathogens and sparing the normal microbiome [1]. These properties make phage therapy a compelling strategy for difficult pediatric infections. The next sections will examine how these principles have translated into clinical practice, focusing on pediatric cases and studies, and evaluate the outcomes and safety observed thus far.

Clinical Applications of Phage Therapy in Pediatric Populations (2015–2025)

Phage therapy has transitioned from theory to practice in a number of notable pediatric cases over the last decade. While no large randomized controlled trials in children have been completed to date, numerous case reports and small case series illustrate the circumstances in which phage therapy has been applied and the results observed. This section presents a detailed overview of the current state of clinical research and applications of phage therapy in pediatric patients, highlighting recent examples from 2015–2025.

Case Reports of Phage Therapy in Children: One landmark pediatric case involved a 15-year-old patient in the United Kingdom with cystic fibrosis who developed a life-threatening disseminated *Mycobacterium abscessus* infection following a double lung transplant. *M. abscessus* is a multidrug-resistant non-tuberculous mycobacterium that is extremely difficult to treat. In 2019, Dedrick, Spencer, and colleagues reported that this patient was treated with a custom cocktail of three bacteriophages that had been bioengineered to efficiently kill her specific *M. abscessus* strain [4]. Phages were administered intravenously over an extended period. The phage therapy was well tolerated with no reported adverse events, and the patient showed remarkable clinical improvement: the infective lesions (including skin nodules) resolved substantially, liver function improved, and even a chronic sternal wound from surgery closed up [4]. This case, published in *Nature Medicine* in 2019, was the first known use of engineered bacteriophages to treat a human mycobacterial

infection and provided a proof-of-concept that phages could be used to treat a severe infection in a pediatric cystic fibrosis patient that was not responding to antibiotics.

Another notable case comes from Australia, where a 7-year-old child had an extensive chronic osteoarticular infection of the hip and femur caused by *Pseudomonas aeruginosa*. The infection persisted despite multiple surgeries and long-term antibiotic therapy, raising concern for catastrophic outcomes (such as sepsis or permanent disability). They described the use of adjunctive phage therapy in this child, alongside continued antibiotics [5]. A lytic anti-*Pseudomonas* phage was administered intravenously, and the dosing was adjusted in real-time based on phage and bacterial levels in the bloodstream [5]. Within two weeks of starting phage therapy, markers of infection began improving significantly, suggesting a therapeutic effect [5]. Notably, the child experienced some transient fever and localized pain early in phage treatment, coinciding with what appeared to be a burst of bacterial lysis and an immune response [5]. These symptoms were self-limited. Over the course of treatment, phage therapy was able to reduce the bacterial burden in the infected bone, and the child's condition improved without further surgical intervention [5]. This case demonstrated that intravenous phage therapy can be combined with antibiotics in a pediatric patient to successfully treat a deep-seated multidrug-resistant infection, with careful monitoring of the host and pathogen response.

Chronic bacterial respiratory infections in children with cystic fibrosis (CF) have also been targets for phage therapy. Aside from the *Mycobacterium* case above, most CF-related phage treatments have focused on *P. aeruginosa* and *Burkholderia cepacia* complex, common causes of lung infections in CF that are often resistant to antibiotics. A small series of pediatric CF patients in Europe received phage therapy via nebulization (inhaled phages) to target *P. aeruginosa* lung infections as part of compassionate use programs. For example, a 17-year-old CF patient in Belgium with a refractory *B. cepacia* infection showed improved lung function and decreased bacterial density in sputum after receiving nebulized phages, as briefly referenced in a 2020 review [6] (detailed case data were limited due to the anecdotal nature of the report). These individual cases suggest potential benefit, but systematic evaluation is needed.

Skin and soft tissue infections in children have likewise been treated with phages, especially when antibiotic options were exhausted. One case from the Eliava Phage Therapy Center in Tbilisi, Georgia, involved a 16-year-old boy with Netherton syndrome (a rare genetic skin disorder) who suffered from chronic, antibiotic-resistant *Staphylococcus aureus* skin infections [7]. The patient had widespread eczema-like lesions colonized by MRSA (methicillin-resistant *S. aureus*) and had allergies to multiple antibiotic classes, severely limiting therapy [7]. He was treated with topical and oral anti-staphylococcal phage preparations. Within one week, the patient showed significant improvement: reduced redness, less exudation, and relief from itching [7]. After six months of ongoing phage therapy (with periodic visits and phage re-supply), his skin condition had stabilized dramatically, infection markers decreased, and quality of life has substantially improved [7]. Importantly, no adverse effects were noted in blood tests or organ function during the 6-month treatment [7]. This compassionate use case underscores the potential of phages to manage chronic infections even in immunocompromised pediatric patients, and it highlights the role of specialized phage centers (like Eliava in Georgia) in providing treatment for patients from countries where phage therapy is not yet accessible.

Beyond individual cases, there have been broader efforts to apply phage therapy in pediatric infections through structured programs or trials. In 2016, a consortium at the University of California San Diego (UCSD) established the Center for Innovative Phage Applications and Therapeutics (IPATH) – the first phage therapy center in North America – after successfully treating a critical adult case and seeing growing demand [8]. Since then, IPATH has coordinated multiple expanded-access phage treatments, some of which included adolescent patients (particularly those with CF and *P. aeruginosa* or *Mycobacterium* infections) [8], [3]. A recent retrospective analysis of 20 compassionate-use phage treatments for antibiotic-refractory mycobacterial infections (primarily *M. abscessus* in CF patients, age range spanning adolescents and young adults) was published in 2023 [3]. In that cohort, phages were administered intravenously and/or by nebulization over an average of six months [8]. Notably, no serious adverse reactions to phage therapy were observed in any of the 20 patients [3]. About 55% of patients (11 out of 20) showed clinical improvement or reduced bacterial load, while the others had either stable disease or no response [3]. Some patients in this series were pediatric (including teenagers with CF), reinforcing that children can be included in phage therapy protocols safely. Another retrospective series of 12 cases (from a different center) including some pediatric patients found a similar outcome: two-thirds (66%) of the treated cases had favorable clinical or microbiological responses, with no major adverse events, and in vitro testing often showed that phages could synergize with antibiotics to enhance bacterial killing [6].

Emerging clinical trials are now starting to formally evaluate phage therapy in infections that often affect children. For instance, a Phase 1/2 trial is underway using a phage cocktail ("ShigActive") for shigellosis (a diarrheal illness that is common in children in some regions), aiming to test safety and efficacy of oral phages against *Shigella* in pediatric patients [9]. Another trial is exploring the use of bacteriophages to modulate the gut microbiome in preterm infants, essentially a form of preventative phage therapy to reduce the risk of necrotizing enterocolitis or other neonatal infections [9]. In respiratory medicine, a trial in 2022 was reported that uses phages targeting *P. aeruginosa* in children with cystic fibrosis to see if phage inhalation can reduce bacterial density and inflammation [10]. Additionally, phage therapy has been proposed for perinatal infections such as neonatal sepsis caused by *Group B Streptococcus*, with animal models and in vitro studies suggesting potential, though human neonatal trials have not yet begun [11]. These research efforts reflect a growing recognition of the unique needs and opportunities for phage therapy in the pediatric population.

In summary, over the past decade there have been numerous compassionate use cases where phage therapy was employed to treat severe, antibiotic-resistant infections in children – ranging from respiratory and bone infections to skin and disseminated infections. The outcomes in these cases have often been positive, with many children experiencing clinical improvements and bacterial clearance that could not be achieved with antibiotics alone. Importantly, these pediatric applications have also provided data on the safety and tolerability of phages in children, which we will examine next. While still mostly anecdotal, the collective experience worldwide sets the stage for more systematic clinical trials to establish efficacy in pediatrics.

Safety, Efficacy, and Tolerance of Phage Therapy in Children

One of the most crucial considerations for any pediatric therapy is safety. The use of bacteriophages in children raises specific questions: Do phages cause any unique adverse reactions in younger patients? How well are phages tolerated, especially when administered systemically? And what is the evidence that phage therapy is effective in resolving infections in children? We address these questions by drawing on published case reports, case series, and the limited clinical trial data available.

Safety and Tolerability: Clinical evidence to date indicates that phage therapy is generally safe and well-tolerated in children, even with prolonged treatment courses. In compassionate use studies comprising both adults and children, serious adverse events attributable to phages have been exceedingly rare [3], [6]. For example, in the 20-patient mycobacterial infection series described earlier, no adverse reactions were attributed to phage therapy in any patient, regardless of the phage used or the route of administration [3]. Similarly, the 12-case series by Green et al. reported no major adverse effects; the authors noted that phages were well tolerated across all cases, consistent with the notion that properly purified phage preparations have low inherent toxicity [6]. These findings align with a larger body of literature: a systematic analysis of 2,241 phage therapy cases (of various ages) found that approximately 79% of patients experienced clinical improvement and 87% achieved infection clearance, *without significant side effects* [9]. Another review focusing on chronic wound infections (some of which were in pediatric burn patients) reported an 86% rate of clinical resolution or improvement with phage therapy and noted no adverse effects in those treated [9]. Collectively, these data suggest that the safety profile of phage therapy is favorable, which is critical for pediatric use. Indeed, bacteriophages have been administered to children as young as infants (for instance, oral phage therapy for infantile diarrhea in some trials) with no reported toxicity, though such studies are still limited in scope.

Phage therapy's good tolerability can be attributed to several factors. Phages are highly specific, so they do not generally harm human cells or disrupt beneficial microbiota extensively [1]. Additionally, phage preparations, when purified correctly, contain minimal bacterial residues or endotoxins that could trigger inflammation[1]. There is, however, one aspect of phage therapy safety that merits attention: the immune response. When a large number of bacteria are lysed rapidly (whether by phages or bactericidal antibiotics), a Jarisch-Herxheimer-like reaction can occur due to the sudden release of bacterial endotoxins and components. In the pediatric Pseudomonas bone infection case, doctors observed transient fevers and inflammatory responses in the first days of phage therapy, which they attributed to rapid bacterial lysis rather than an allergic reaction [5]. These symptoms were managed supportively and were not long-lasting. Additionally, because phages are foreign proteins, the human immune system may generate anti-phage antibodies over time. In the 20-patient series, 8 patients developed measurable neutralizing antibodies against the phages during therapy, and in about 4 cases this might have reduced the treatment efficacy [3]. Importantly, even when anti-phage antibodies arose, they did not cause allergic reactions or illness; the main consequence was that the phages could be cleared faster from circulation. In practice, clinicians can sometimes overcome this by using higher

phage doses, switching to a different phage, or combining routes of administration (e.g., both local and systemic) to achieve the desired antibacterial effect.

From a pediatric tolerability standpoint, routes of phage administration are an important consideration. Phages have been given orally, topically, inhaled via nebulizer, and intravenously to children. Oral phage therapy (for gut infections) and topical phage use (for wound or skin infections) tend to be very well tolerated, with essentially no difference from placebo in terms of subjective side effects in small trials [9]. Intravenous phage therapy, which might be expected to pose higher risks, has surprisingly also shown a strong safety record when done under compassionate use protocols with appropriate manufacturing (often meeting sterility and endotoxin standards similar to IV medications) [6]. For instance, the first U.S. intravenous phage therapy case in 2016 (an adult case) set a precedent: no infusion reactions occurred [8], leading the way to more IV phage uses in subsequent pediatric cases (such as the *M. abscessus* and *Pseudomonas* cases detailed earlier, both of which tolerated IV phage infusions without complications). The lack of allergic or anaphylactic reactions in reported pediatric phage therapy cases is reassuring, though continued vigilance is warranted as the number of treated children grows.

Efficacy in Treating Resistant Infections: Evaluating the efficacy of phage therapy is challenging due to the individualized nature of treatments and the lack of large trials. However, the collective case data provide evidence that phages can contribute significantly to clearing infections in children who have exhausted antibiotic options. In many of the cited pediatric cases, phage therapy led to outcomes that were unachievable with prior antibiotics alone – for example, resolution of a months-long infection or improvement in organ function [4], [5]. In the cystic fibrosis lung transplant patient with disseminated *M. abscessus*, phages were deemed the critical factor that finally brought the infection under control, as multiple antibiotics had failed before [4]. In the Netherton syndrome case, phage therapy controlled chronic *S. aureus* skin colonization and significantly improved eczema lesions where years of antibiotics had not [7]. These are anecdotal successes, but they align with broader statistics: across published phage therapy cases (adult and pediatric), roughly 50–80% report some level of clinical or microbiological improvement [6], [9]. A review in 2021 (Pirnay et al., *Lancet Infectious Diseases*) examining difficult-to-treat infections found about two-thirds of patients had favorable outcomes after phage therapy, which mirrors the 66% success rate in Green et al.'s 12-patient series [6].

It is important to note that phage therapy is usually not used in isolation. In nearly all pediatric cases, phages were administered in conjunction with standard of care antibiotics (often because completely stopping antibiotics would be unethical in a serious infection). This makes it hard to disentangle the contribution of phages versus antibiotics. Nonetheless, in cases where patients had shown no improvement on antibiotics alone for weeks or months, the addition of phages coincided with recovery, suggesting phages provided a decisive synergistic effect [6]. Laboratory studies corroborate this synergy: phages and certain antibiotics can work together to kill bacteria more effectively than either alone, a phenomenon termed phage-antibiotic synergy [6]. This has been observed with various combinations (e.g., phages plus ciprofloxacin against *P. aeruginosa*) and may help prevent or overcome phage resistance during therapy [6].

Long-term efficacy, i.e., whether phage therapy leads to durable cures, is another question. Some children who benefited from phage therapy remained infection-free long after treatment (e.g., patient with the *M. abscessus* infection was reported clear of infection one year post-treatment) [4], whereas others needed repeated phage administration to keep chronic infections at bay (the Netherton syndrome case required ongoing phage use to suppress *S. aureus* over 6+ months [7]). These patterns are analogous to antibiotic therapy: some infections are cured by a single course, others require long-term suppressive therapy. Phages, when used appropriately, can be integrated into such strategies. Notably, because phages do not seem to carry significant toxicity, prolonged or intermittent use (even over months) in children has been reported without harm [7], which is encouraging for chronic infection management.

Immune Considerations: Pediatric patients, especially young children, have developing immune systems that might respond differently to phage therapy than adults. While no phage-specific immune differences have been conclusively identified between children and adults, one could hypothesize that children might have less prior exposure to environmental phages and therefore fewer pre-existing antibodies. This could mean initial phage treatments in children are less likely to be neutralized by the immune system. On the other hand, children (particularly those with inflammatory conditions) might be more prone to robust cytokine responses during infection treatment. The limited data so far show that children generally handle phage therapy without excessive immune-mediated complications [5], [7].

In conclusion, current evidence suggests that phage therapy can be both safe and effective in children with antibiotic-resistant infections. The majority of pediatric patients in case studies have tolerated phages with

minimal side effects, and a significant proportion have derived clinical benefit, clearing infections that were otherwise unresponsive to treatment. These findings are promising, but they come with the caveat that most evidence comes from uncontrolled compassionate use scenarios. To truly establish the efficacy of phage therapy in pediatrics, controlled studies and clinical trials will be necessary. Nonetheless, for children facing life-threatening resistant infections today, phage therapy under compassionate use remains a valuable option with a favorable risk-benefit profile.

Challenges in Implementing Phage Therapy

Despite the encouraging results seen in individual cases, there are several challenges to broader implementation of phage therapy, particularly in pediatric clinical practice. These challenges span scientific, logistical, regulatory, and ethical domains. Here we discuss the major hurdles: (1) regulatory and approval issues, (2) production and formulation of phage therapeutics, (3) bacterial resistance and phage selection, and (4) practical considerations such as financial and logistical barriers.

Regulatory and Legal Hurdles: One of the foremost barriers to implementing phage therapy is the lack of a clear regulatory pathway for approval of phage products. In most countries, phages are not yet approved as licensed medical treatments (with a few exceptions in parts of Eastern Europe and the former Soviet Union). Instead, therapeutic phages are typically provided under experimental or compassionate use frameworks. For example, in the United States, each use of phages in a patient usually requires an FDA-approved single-patient Investigational New Drug application, as was done for the cases handled by IPATH at UCSD [3], [6]. This process can be time-consuming, requiring scientific justification and review for each patient, which is not conducive to emergency treatment. In the European Union, regulations have also been strict, but there have been moves to accommodate phage therapy via "magistral preparations" (custom-made medicines for individual patients prepared in a pharmacy) in countries like Belgium effectively allowing phage preparations on a case-by-case basis without full market authorization. In Poland, phage therapy is explicitly classified as an “experimental treatment” under a 1996 law, which permits its use by medical professionals within a supervised experimental protocol [9]. The Ludwik Hirszfeld Institute in Wrocław operates under this framework, treating patients with phages on a compassionate basis while adhering to ethical guidelines like the Declaration of Helsinki [12,13]. Such national regulatory allowances have been crucial in keeping phage therapy alive in certain regions, but they also mean that phages are not part of the standard pharmacopeia and access is limited.

A complicating factor is that naturally occurring phages, being biological entities found in nature, are generally not patentable in their native form [14,15,16]. Pharmaceutical companies thus have little incentive to invest in expensive clinical trials for a product they cannot exclusively market. To generate return on investment, companies may resort to engineering phages (which can be patented) or patenting proprietary cocktails or manufacturing processes [14,15,16]. This situation has led to a relative dearth of commercial interest, slowing development. Regulatory agencies are still grappling with how to classify phages as drugs, biologics, or something unique. The complexity is increased when dealing with personalized phage therapy (tailoring a phage to each patient’s bacterial isolate) because each preparation might be considered a distinct product. Recent discussions between phage researchers and regulators have aimed to find a middle ground, such as master files for phage libraries and adaptive trial designs [14,15,16]. Nevertheless, until a more straightforward regulatory framework is established, phage therapy implementation will likely be restricted to experimental use, making it challenging to integrate into routine pediatric care.

Production and Quality Control: Manufacturing bacteriophages for therapeutic use presents its own set of challenges. Phages must be produced by growing their host bacteria, and then the phage lysate has to be purified to remove bacterial debris (endotoxins, proteins, DNA) to avoid causing inflammation when administered to patients [1]. Achieving high purity and high titer (concentration) is essential for safety and efficacy. This process can be technically demanding and time-consuming, especially for phages that have not yet been produced under Good Manufacturing Practice (GMP) conditions. When a child has a critical infection, waiting weeks to manufacture a personalized phage under GMP may not be feasible. Some phage centers maintain ready-to-use phage libraries for common pathogens (such as *Staphylococcus aureus*, *Escherichia coli*, *P. aeruginosa*) which can speed up the process, if the patient’s bacterial isolate is susceptible to one of those phages, treatment can start quickly. However, for uncommon pathogens, new phages might need to be isolated from the environment (sewage, water, soil samples) and then tested, which is a research endeavor not a standard hospital practice.

Another production challenge is formulation: delivering phages to the infection site in the body. Different infections require different delivery methods (oral, topical, IV, inhaled), and phages may need formulation in a stable medium (buffer, or a cream for skin, etc.). Stability of phages can be an issue; they are generally stable under refrigeration, but extreme temperatures can inactivate them, and they may have limited shelf lives depending on the preparation. Ensuring that phage preparations remain potent throughout treatment (which could last months) is important. There has been progress in lyophilizing (freeze-drying) phages for storage and in encapsulating phages for targeted delivery (for instance, gastro-resistant capsules that release phages in the intestines). For pediatric use, palatability and ease of administration also matter e.g., developing phage cocktails that can be given as a tasty oral syrup for children, or nebulizer solutions that a child can inhale without irritation.

Bacterial Resistance to Phages: Just as bacteria can become resistant to antibiotics, they can also evolve resistance to phages. This typically occurs through mutations that alter the phage's binding site on the bacterial surface, production of enzymes that degrade phage DNA, or other anti-phage defense systems in bacteria. The specter of resistance means that a phage that works today might not work tomorrow if the bacterial population adapts. However, there are strategies to mitigate this issue. One approach is to use phage cocktails – mixtures of multiple phages that target the same bacterium via different receptors. The chance of a bacterium simultaneously developing resistance to several phages is much lower than to a single phage. Many of the compassionate treatments (including pediatric cases) used phage cocktails precisely for this reason. For instance, the *M. abscessus* patient was treated with a cocktail of three phages [4]; if the bacterium had mutated to resist one phage, the others could still infect it. In practice, the *M. abscessus* isolate did not develop phage resistance during therapy [3], and no phage resistance emerged in any of the 11 single-phage-treated patients in the 20-patient series [3]. Another strategy is sequential therapy: if resistance to one phage arises, new phages can be isolated or engineered to infect the resistant strain, creating an iterative treatment plan. This "evolution in real-time" approach leverages the vast diversity of phages in nature; researchers can usually find a new phage for a resistant bacterium given sufficient time [1]. Indeed, unlike the fixed chemical structure of an antibiotic (which, once bacteria become resistant, is difficult to modify quickly), phages are part of an evolutionary arms race and can be selected or modified to catch up to bacterial changes [6].

That said, monitoring for phage resistance requires good microbiology support. Clinicians need access to labs that can culture the pathogen during treatment and test if it remains phage-susceptible. Not all hospitals have this capability yet. Moreover, if a patient's infection involves multiple bacterial species (common in conditions like cystic fibrosis lung disease), phage therapy might need to address each pathogen, complicating the regimen with multiple phages.

Financial and Logistical Challenges: Implementing phage therapy for children at world scale requires addressing cost and access. Currently, many phage treatments in Western countries are performed in academic or research settings, often funded by grants or on a compassionate, non-profit basis. The actual cost of producing a phage therapy for one patient can be high – involving laboratory work, personnel, and often custom preparations. Without insurance reimbursement or government funding, this is not sustainable on a larger scale. Additionally, there are few experts trained in phage therapy, meaning that most physicians have little to no experience with prescribing or monitoring phage treatments. Education and training would be needed to spread competence in this area. Ethically, questions have been raised about equity of access: will phage therapy be available only at specialized centers and to those who can afford to travel or pay, or will it be integrated into standard healthcare systems? These questions remain to be fully answered, but interest in phage therapy is increasing among clinicians, and patient advocacy for phage options is growing [17,18,19,20]

In summary, implementing phage therapy beyond experimental use faces significant hurdles. Regulatory paths are still being forged, production needs to be standardized and scaled up, and strategies to manage phage-bacteria dynamics (like resistance) must be in place. Overcoming these challenges will likely require concerted efforts by scientists, regulatory agencies, healthcare providers, and policymakers. A combination of more clinical trial data (to convince regulators and providers), innovative business models or public funding (to address the economic issues), and international collaboration (to share phage resources and knowledge) will pave the way for phage therapy to become a more routine part of pediatric infection management in the future.

Conclusion and Future Directions

Phage therapy in children with antibiotic-resistant infections represents both a revival of an old antimicrobial strategy and a frontier of modern medicine. This review has outlined the significance of phage therapy as a response to the escalating crisis of antibiotic resistance, especially for vulnerable pediatric patients who may run out of conventional treatment options. Bacteriophages offer a targeted mechanism of action, leveraging their natural life cycle to destroy pathogenic bacteria while sparing the normal flora [1]. Compared to traditional antibiotics, phages bring unique advantages such as auto-dosing at the infection site and lack of cross-resistance with antibiotic-resistant bacteria [1]. At the same time, deploying phage therapy requires careful consideration of its differences – from ensuring a matching phage for the pathogen to navigating patient immune responses and regulatory hurdles.

The current state of clinical research, as surveyed from 2015–2025, provides cautious optimism. Numerous pediatric case reports and small series have documented successful phage therapy outcomes in life-threatening infections, ranging from multi-drug-resistant *Pseudomonas* and *Staphylococcus* infections to atypical mycobacterial diseases. Children who had poor prognoses under antibiotic therapy alone often improved when phages were introduced, with some cases resulting in complete resolution of infection [4], [5]. These anecdotal successes, backed by data showing two-thirds or more of patients benefiting in compiled analyses [6], [9], suggest that efficacy is real in at least a subset of cases. Importantly, the safety and tolerability profile of phage therapy in children has been favorable: adverse effects are generally mild and infrequent, with no serious toxicity observed in reported pediatric uses [3], [6]. Even prolonged phage treatments have been carried out in children without harming organ function or development [7]. This supports the notion that phage therapy, when produced and administered under appropriate standards, can be a safe adjunct or alternative in pediatric infectious disease care.

However, the journey to making phage therapy a mainstream treatment for children (or adults) is not straightforward. We have highlighted several challenges: regulatory approval remains the largest barrier, as no major regulatory agency has yet formally approved a bacteriophage product for general use in infections. Without such approval, phage therapy will continue to rely on individualized compassionate use exemptions, which limits the number of patients who can benefit. Therefore, a crucial future step is conducting well-designed clinical trials that can provide the evidence necessary for regulatory bodies to evaluate phage therapy. These trials should ideally be multicenter and include pediatric arms if possible, to directly assess efficacy and safety in children. Conditions that could be targeted in trials include pediatric burn wound infections (phages vs. standard care), pediatric diarrheal infections (phages vs. placebo for rotavirus-negative bacterial diarrhea), or adjunct phage therapy in pediatric cystic fibrosis lung infections (phages plus antibiotics vs. antibiotics alone). Two of seven modern phage therapy trials to date have shown positive efficacy results [9], indicating that with refined trial design and phage preparations, success is attainable.

Another priority for future research is understanding and optimizing phage-host interactions in the human body. This includes studying the pharmacokinetics of phages in pediatric patients: how long do they persist, what tissues do they penetrate, and how does the immune system modulate their activity? Pharmacodynamic modeling (perhaps through animal studies or innovative in vitro setups) can inform dosing regimens to maximize efficacy (for example, whether multiple daily phage doses are needed or if once daily is sufficient given phage replication). Additionally, genomic and engineering approaches to phage development hold promise. Researchers are exploring genetically engineered phages that can overcome bacterial defense systems or deliver biofilm-degrading enzymes. These could be especially helpful in pediatric infections like CF lung disease where biofilms are problematic.

In terms of practical implementation, efforts are needed to create phage libraries and production pipelines that can rapidly provide personalized phage therapies. In the near future, we may see regional phage banks that hospitals can query when a patient has an MDR infection – if a matching phage is found, a vetted preparation could be dispatched quickly. This kind of system would make phage therapy far more accessible.

Addressing the economic and industry aspect is also a part of the future outlook. Incentives for phage development, possibly through public-private partnerships or government grants, might be necessary since traditional patent-driven investment is less effective for phages [13]. Alternatively, compounding pharmacies and hospital pharmacy departments could take on phage preparation as a service, integrating it into healthcare without the need for large pharmaceutical involvement.

In conclusion, phage therapy for pediatric antibiotic-resistant infections stands at a pivotal juncture. The accumulated evidence from 2015–2025 paints a picture of a potent tool that has already rescued some children from otherwise intractable infections, with minimal downsides observed. The challenge ahead lies in

transitioning from these individual successes to a validated, regulated treatment option available to all children who might benefit. This will require continued research to address open questions (efficacy, optimal usage, long-term outcomes), investment in production and delivery mechanisms, and progressive regulatory thinking to accommodate a novel therapeutic approach. If these hurdles can be overcome, bacteriophages may well become an integral part of the pediatric infectious diseases arsenal in the coming decades – fulfilling a century-old promise in the era of antibiotic resistance.

Author's contribution:

Conceptualization, Magda Skudzińska; methodology, Magda Skudzińska and Kamil Rajczyk; investigation, Filip Kochański, Magdalena Bartold, and Julia Ceryn; formal analysis, Julia Ceryn and Katarzyna Kopeć; resources, Aleksandra Jaskulska and Janina Pohrybieniuk; data curation, Karolina Wołk and Janina Pohrybieniuk; writing – original draft, Magda Skudzińska and Kamil Rajczyk; writing – review and editing, Katarzyna Kopeć and Jan Pietrzak; visualization, Magdalena Bartold and Karolina Wołk; supervision, Jan Pietrzak and Aleksandra Jaskulska; project administration, Kamil Rajczyk and Filip Kochański. All authors have read and agreed with the published version of the manuscript.

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