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Review article

Hydrogel-based local delivery of bacteriophages for infection control: a systematic review of *in vivo* evidence

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ABSTRACT

Background: Localized biofilm-associated infections remain difficult to treat with systemic antibiotics amid rising resistance. Hydrogel delivery may enhance bacteriophage (phage) therapy by protecting phages, prolonging residence, and enabling controlled release. This systematic review summarizes *in vivo* evidence for hydrogel-mediated phage delivery and its translational relevance.

Methods: Following PRISMA 2020, PubMed, Web of Science were searched to 14 January 2026 using MeSH terms for bacteriophages, hydrogels/local delivery, and *in vivo* or clinical applications. Eligible studies reported original *in vivo* animal or human data; *in vitro*-only work was excluded.

Results: Nineteen studies met criteria: three clinical and sixteen preclinical. Clinical use included fracture-related infection, burn wound, and prosthetic joint infections treated with commercially available phage preparations in hydrogels. In a single compassionate-use fracture-related infection case managed with concurrent surgical debridement and systemic antibiotics, infection control without recurrence and good bone was were observed at one year; locally applied phages remained detectable for approximately 72 h, indicating *in vivo* release and surgical compatibility, although the independent contribution of the hydrogel–phage component could not be isolated. Preclinical studies tested 28 phages against six bacterial species via topical, injected, intraoperative, oral, or irrigation delivery. Consistent benefits occurred in burn wound infection ($n = 6$) and wound/soft-tissue infection models ($n = 5$) with lower bacterial load, improved healing, and increased survival in two burn wound infection studies. Bone/joint models ($n = 4$) showed partial reduction but inconsistent eradication. Other studies demonstrated ~2000-fold pathogen reduction in colitis and decreased bacterial and inflammatory markers in endodontic infection.

Conclusions: Hydrogel-based local phage therapy is a feasible strategy for infection control No major adverse effects were reported in the included studies, although safety reporting was limited. Standardized *in vivo* comparisons and clinical trials are needed to optimize delivery and dosing.

1. Introduction

The rapid global escalation of antimicrobial resistance (AMR) has rendered many conventional antibiotics ineffective, particularly in the context of localized, biofilm-associated infections such as chronic wounds, osteomyelitis, and implant-associated infections [1]. These

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conditions are frequently characterized by high bacterial burden, spatially constrained infection niches, impaired vascularization, and recalcitrant biofilms—all of which severely limit the efficacy of systemic antimicrobial therapy [2]. As a result, there is an urgent clinical need for alternative or adjunctive antimicrobial strategies capable of achieving high local potency while minimizing systemic toxicity and off-target effects.

Bacteriophage (phage) therapy has re-emerged as a promising precision antimicrobial approach due to the inherent specificity, self-amplifying nature, and activity against antibiotic-resistant bacteria. As sustained presence and contact between phages and bacterial targets are essential for therapeutic success, the local application has the advantaged of enhanced retention, stability, and biofilm penetration [3].

In this context, hydrogels are considered as highly attractive delivery carriers for local bacteriophage therapy. Hydrogels are three-dimensional, water-rich polymeric networks that can be engineered to mimic the mechanical and biochemical properties of native tissues while providing a protective microenvironment for sensitive biological components [4]. Their tunable physicochemical properties—including porosity, degradation kinetics, injectability, and stimuli responsiveness—enable controlled and localized release of encapsulated phages directly at the site of infection [5].

Over the past decade, a growing body of *in vivo* evidence has demonstrated the therapeutic potential of phage-loaded hydrogels across diverse infection models and multidrug-resistant pathogens such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Enterococcus faecalis*, and *Klebsiella pneumoniae* [6].

Despite this expansion of the field, the existing literature remains fragmented, with substantial heterogeneity. Moreover, many reviews to date have emphasized material design or *in vitro* performance. The aim of this systematic review is to critically evaluate the *in vivo* evidence for hydrogel-based delivery systems used in local bacteriophage therapy, with a specific emphasis on translational applicability and clinical relevance.

2. Methods

2.1. Search strategy

This work constitutes a systematic review following the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [7]. A comprehensive literature search was performed in two major bibliographic databases (PubMed and Web of Science) to identify relevant studies investigating hydrogel-based local delivery of bacteriophages *in vivo*. Searches were conducted without restrictions on publication year to capture both foundational and recent studies. The search included all articles published up to 14 January 2026. Only articles published in English were considered. The search strategy combined Medical Subject Headings (MeSH) and free-text terms for three concepts: (i) bacteriophages, (ii) hydrogels or local delivery systems, and (iii) *in vivo*, animal, or clinical infection models. The full PubMed query was:

(bacteriophage*[Title/Abstract] OR "phage therap*"[Title/Abstract] OR "Bacteriophages"[MeSH]) AND (hydrogel*[Title/Abstract] OR gel-based[Title/Abstract] OR "polymer gel*"[Title/Abstract] OR "local deliver*"[Title/Abstract] OR "controlled release"[Title/Abstract]) AND (*in vivo*[Title/Abstract] OR clinical[Title/Abstract] OR "case report*"[Title/Abstract] OR "compassionate use"[Title/Abstract] OR "animal model*"[Title/Abstract] OR murine[Title/Abstract] OR larvae[Title/Abstract]).

An equivalent topic search (TS=) using the same three concept blocks combined with the AND operator was run in Web of Science. The complete, database-specific search strings are provided in Supplementary Table S1.

2.2. Selection criteria

Studies were screened in two stages by two independent reviewers. First, titles and abstracts were assessed for relevance. Full texts of potentially eligible studies were then retrieved and evaluated against the predefined inclusion criteria. Studies were included in the review if they met the following criteria: (1) Investigated hydrogels as delivery system for bacteriophages, (2) Presented original *in vivo* experimental data, and (3) were available as full-text. Studies reporting on phage-mediated killing and reactive oxygen species (ROS) [8] were excluded for the scope of this article. During the screening stage, 329 records were excluded because they did not meet the inclusion criteria, primarily due to absence of either phage or hydrogel application or investigations *in vitro* only. All records could be retrieved and assessed for eligibility. One study reporting on the phages LPS-5, LUZ24, PAML-31-1 and Omko1 in *Pseudomonas aeruginosa* wound infection was excluded as it was available as preprint only [9].

2.3. Data analysis

A quantitative meta-analysis was not feasible because of inconsistent outcome reporting, non-standardized infection models, and the absence of variance estimates in most studies. Statistical heterogeneity was therefore not formally quantified, and a structured narrative synthesis was performed.

3. Results

3.1. Study selection and characteristics of included studies

The database search identified 430 records (PubMed $n = 262$; Web of Science $n = 168$). After removal of 81 duplicates, 349 records were screened by title and abstract. Of these, 329 were excluded because they did not meet the inclusion criteria, primarily due to absence of bacteriophage or hydrogel use or because studies were limited to *in vitro* experiments. Twenty full-text articles were assessed for eligibility, and one preprint-only study was excluded. A total of 19 studies were included in the qualitative synthesis (Fig. 1).

Of the included studies, three reported clinical applications (Table 1) and sixteen were preclinical *in vivo* animal studies The studies covered multiple infection indications, including burn wound infection, cutaneous wound and soft tissue infection, fracture-related infections and implant-associated infections, osteomyelitis, gastrointestinal infection, and endodontic infection. Across the preclinical studies, 28 distinct bacteriophages targeting six bacterial species were evaluated using topical, intraoperative, locally injected, irrigation, and oral delivery approaches. Natural polymer hydrogels (e.g., alginate, carboxymethyl cellulose, chitosan) were most frequently used, followed by synthetic polymer hydrogels (e.g., polyvinyl alcohol, PEG) and hybrid lipid–hydrogel systems (Table 2).

3.2. Clinical evidence

Alt et al. (2024) reported a compassionate-use case in which local bacteriophage therapy was added to surgical management of a fracture-related infection case caused by polymicrobial, multi drug-resistant bacteria. Phages were incorporated into a Defensive Antibacterial Coating (DAC®) hydrogel and applied locally to fixation hardware during reconstruction surgery, alongside standard surgical and antibiotic treatment. Using metagenomic sequencing and qPCR of post-operative wound drainage, the authors demonstrated a time-limited release and detectability of phages *in vivo*, peaking early after surgery and disappearing within approximately 72 h. The patient showed no infection recurrence and good bone healing at one year, supporting the feasibility and safety of local hydrogel-based phage delivery [10]. Beschastnov and colleagues investigated the use of ex tempore

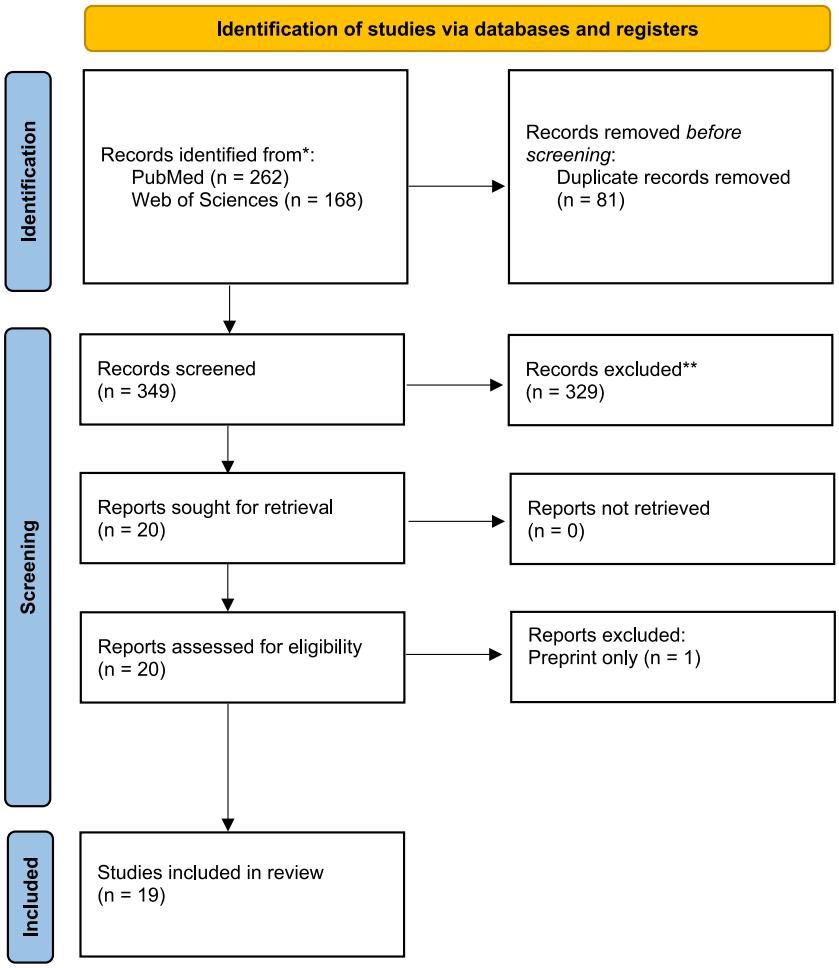

Fig. 1. PRISMA 2020 flow diagram for new systematic reviews [7].

Table 1
Clinical reports of hydrogel-based local bacteriophage therapy (two compassionate-use case reporta, and one prospective cohort study).

Author, Year	Origin	Study design	Phages	Phage source	Pathogen	Indication
Alt et al., 2024 [10]	Germany	Compassionate-use case report	Intesti	Eliava Institute	*Pseudomonas aeruginosa*, *Proteus mirabilis*, *Enterococcus faecium*, *Klebsiella pneumoniae*, *Escherichia coli*	Fracture-related infection
Beschastnov et al., 2023 [11]	Russia	Prospective cohort study	PYO	Mikrogen	*Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Enterobacter cloacae*, *Escherichia coli*	Burn wound infection
Ferry et al., 2020 [12]	France	Compassionate-use case report	PP1815, PP1493	Phaxiam Therapeutics	*Staphylococcus aureus*	Prosthetic joint infection

polyvinyl-alcohol (PVA) hydrogel dressings saturated with bacteriophage suspensions to sanitize burn wound infections ahead of free split-thickness skin grafting in a prospective cohort study. Patients treated with phage-loaded hydrogel dressings showed similar bacterial contamination levels to controls treated with systemic antibiotics, but improved indicators of proliferative activity and angiogenesis at the graft site and slightly better graft engraftment outcomes, suggesting that the phage hydrogel is safe and may support wound healing without cytotoxic effects [11].

Ferry and colleagues reported a single salvage case in which a bacteriophage cocktail was mixed into DAC® hydrogel and applied locally during a debridement, antibiotics, and implant retention (DAIR) procedure to treat a relapsing *Staphylococcus aureus* knee megaprosthesis infection without loosening. The phages were selected after susceptibility testing and *in vitro* release from the hydrogel was rapid with stable titers for hours, supporting feasibility of the delivery approach. Post-surgery, the patient initially showed a favourable local wound appearance but subsequently experienced an unrelated myocardial infarction and further complications that culminated in transfemoral amputation several months later. This case therefore illustrates the procedural feasibility of incorporating phages into hydrogel during a DAIR procedure, but its ultimately unfavourable limb outcome precludes any inference regarding clinical efficacy [12].

3.3. Preclinical evidence

3.3.1. Burn wound infection

Burn wound infection was the most frequently studied indication ($n = 6$). Across all studies, topically applied phage-loaded hydrogels were associated with improved wound healing outcomes [13,14,23,26–28]. Increased maturation of dermal collagen fibers was reported explicitly by Elshamy et al. [14], while attenuation of infection-associated histopathology and reduced inflammation were described by Sherif et al. [13] and Dehari et al. [26]. Reduced bacterial burden was consistently

Table 2
In vivo studies evaluating hydrogel-based local delivery of bacteriophages across infection models.

Author, Year	Origin	Phages	Pathogen	Hydrogel composition	Indication	Species, route of administration	Compared to	Main finding
Yang et al., 2025 [21]	China	LPST83, LPST94, LPST153	*Salmonella Typhimurium*	sodium alginate, hyaluronic acid, Eudragit S100	Colitis	Mice, oral	Pure hydrogel, free phages, PBS, untreated, non-infected	phage-loaded microspheres (HMs-Phages) reduced the intestinal burden of the pathogen (≈2000-fold), lowered pro-inflammatory cytokines, and ameliorated colitis symptoms
Sherif et al., 2025a [13]	Africa	Salmonella_phage_VB_ST-SA173	*Acinetobacter baumannii*, Carbapenem-resistant	Carbopol 940	Burn wound infection	Rats, topical	Pure hydrogel, Gentamicin 0.1%,beta sitosterol (Mebo®) untreated, non-infected	attenuation of infection-associated pathology after 14 days
Elshamy et al., 2025 [14]	Africa	vB_AbaM-SPA vB_AbaM-SPB	*Acinetobacter baumannii*, Carbapenem-resistant	Carboxymethyl cellulose 5% *w/v*	Burn wound infection	Rats, topical	Pure hydrogel, Silverburn®, untreated, non-infected	significant acceleration in the production of dermal mature collagen fibers, enhanced survival rates, improved wound healing
Sherif et al., 2025b [23]	Africa	VB_AB_Acb75	*Acinetobacter baumannii*	Carbopol 940	Burn wound infection	Rats, topical	Pure hydrogel, Gentamicin 0.1%, beta sitosterol (Mebo®) untreated, non-infected	Reduced bacterial load, improved wound healing
Harshitha et al., 2025 [15]	India	BPK01	Klebsiella pneumonia, Carbapenem-resistant	2% aqueous solution of low molecular weight chitosan, acetic acid (1.5% w/v), NaOH, 1% (v/v) of a 25% (v/v) glutaraldehyde solution	Wound infection	Mice, subcutaneously Injected (early and delayed intervention group)	Saline, untreated	Reduced bacterial load, improved wound healing
Abed et al., 2024 [24]	Iran	SAM-E.f 12	*Enterococcus faecalis*	sodium alginate, carboxymethyl cellulose, hyaluronic acid	Wound infection	Mice, topical	Pure hydrogel, free phages, sterile destilled water, untreated, non-infected	Reduced bacterial load, improved wound healing
Vacek et al., 2024 [25]	Czech Republic	812	*Staphylococcus aureus*, Methicillin-resistant	Gum karaya, polyvinyl alcohol, anhydrous glycerol	Wound infection	Pigs, topical	Pure hydrogel, untreated	Reduced bacterial load, improved wound healing, no side effects
Chen et al., 2023 [17]	Switzerland	FJK.R9–30, MK.R3–15	*Pseudomonas aeruginosa*	soy phospholipids (1.2 w/v%), soybean oil (10 w/v%), glycerine (2.3 w/v%), ultrapure water (64 w/v %) + alginate microbeads	Fracture-related infection	Mice, injected (at infection site), w/wo systemic antibiotics	Free phages + systemic antibiotics, ciprofloxacin and meropenem (i.v), untreated	Reduced bacterial load, no complete eradication of infection
Dehari et al., 2023 [26]	India	BPSAΦ1, BPPAΦ1	*Staphylococcus aureus*, *Pseudomonas aeruginosa*	SEPINEO™ P600 (2.5% v/v of total formulation), 0.5% of	Burn wound infection	Rats, topical	silver sulfadiazine, SSD 1.0% (Silvadene®), untreated	improved wound healing reduced inflammation, increased oxygen saturation

(*continued on next page*)

Table 2 (*continued*)

Author, Year	Origin	Phages	Pathogen	Hydrogel composition	Indication	Species, route of administration	Compared to	Main finding
				sterilized glycerol + chitosan microparticles				
Kheljan et al., 2023 [16]	Iran	PA19, PB10	*Pseudomonas aeruginosa*	sodium alginate, carboxymethyl cellulose, $CaCl_2$	Wound infection	Rats, topical, w/ wo antibiotics	Pure hydrogel, hydrogel with antibiotics, non-infected, untreated	Wound healing similar compared to antibiotic-containing hydrogels, best performance with phage–antibiotic hydrogel
Mabrouk et al., 2022 [27]	Africa	vB_Pae_SMP1, vB_Pae_SMP5	*Pseudomonas aeruginosa*, Carbapenem-resistant	5% w/v carboxymethyl cellulose	Burn wound infection	Rats, topical	Pure hydrogel, silver sulfadiazine 1% (Silvirburn®), Collagenase 0.6 IU (Iruxol ®), non-infected, untreated	Improved wound healing and survival
Onsea et al., 2021 [20]	Belgium	ISP	*Staphylococcus aureus*, Rifampicin-resistant	soy phospholipids (1.2%), soybean oil (10%), glycerin (2.3%), water for injection (64%), carboxymethyl cellulose (3%)	Fracture-related infection	Rabbits, intraoperatively vs. subcutaneous access tube	Free phages, systemic antibiotics	Trend of bacterial load reduction on the implant with the phage-loaded hydrogel, no superior effect of compared to antibiotic treatment alone. The application of phage in saline through a subcutaneous access tube was complicated by superinfection and the development of neutralizing antibodies
Wroe et al., 2020 [19]	USA	ΦK ΦPaer4, ΦPaer14, ΦPaer22, ΦW2005A	*Pseudomonas aeruginosa*	4.0% wt/vol poly(ethylene glycol)-4-maleimide	Infected radial segmental defect	Rabbits, intraoperatively	Untreated	Reduced bacterial load (4.7-fold, $\approx 7.4 \times 10^3$ CFU / implant)
Kaur et al., 2019 [28]	India	MR10	*Staphylococcus aureus*, Methicillin-resistant	polyvinyl alcohol 10%, sodium alginate 3%, $CaCl_2$	Burn wound infection	Mice, topical, w/ wo antibiotics	Minocycline, untreated	Improve wound healing
Shlezinger et al., 2019 [22]	Israel	EFLK1, EFDG1	*Enterococcus faecalis*	poloxamer P407	Root canal infection	Rats, irrigated, w/wo antibiotics	free phages, saline	Reduced bacterial load, reduced periapical inflammation
Cobb et al., 2019 [18]	USA	CRISPR-Cas9 modified phage	*Staphylococcus aureus*	3% alginate mixture (w/v)	Osteomyelitis, skin and soft tissue infection	Rats, injected (in bicortical defect space)	Pure hydrogel, hydrogel with antibiotics, PBS, untreated	Improved wound healing, no complete eradication of bone infection

reported across the included studies [13,14,23,26–28], and two studies documented improved survival or reduced mortality in treated animals [14,27]. Comparative performance against standard-of-care topical agents (silver sulfadiazine, gentamicin, or β-sitosterol) was evaluated in four studies, with phage-loaded hydrogels reported as at least non-inferior to these comparators [13,23,26,27]. No major phage- or hydrogel-related adverse effects were reported in these models; however, safety assessment was generally limited and follow-up short, so the absence of reported events should not be equated with demonstrated safety.

3.3.2. Skin and soft tissues infections

Five studies investigated phage-hydrogel therapy in cutaneous wound infection models distinct from burns. All five reported reduced bacterial burden at the infection site following local phage delivery [15,16,18,24,25]. Improved wound healing parameters—including faster closure, improved epithelialization, and reduced inflammation—were observed in four of five studies [15,18,24,25]. One study reported wound healing outcomes comparable to antibiotic-containing hydrogels, with the greatest benefit observed in the phage–antibiotic combination arm [16]. The models spanned different host species (mice [15,24], rats [16,18], and pigs [25]. As with the burn wound studies, no major treatment-related adverse effects were reported, but systematic safety endpoints were rarely predefined.

3.3.3. Bone and joint infection

Four studies evaluated hydrogel-based phage delivery in deep orthopedic infection models, including fracture-related infection [17], osteomyelitis [18], and segmental bone defects [19]. In these studies, local phage delivery via hydrogels consistently reduced bacterial burden on implants and/or surrounding soft tissue. However, complete eradication of infection was not achieved in the study by Chen et al. [17] and Cobb et al. [18] and Onsea et al. noted no superior effect of compared to antibiotic treatment alone. Also, in the latter study, the application of phage in saline through a subcutaneous access tube was complicated by superinfection and the development of neutralizing antibodies [20].

3.3.4. Gastrointestinal infection

The effect of phage-loaded hydrogels on colitis was evaluated in one study. Yang and colleagues reported the development of pH-responsive oral hydrogel microspheres composed of sodium alginate, hyaluronic acid, and Eudragit S100, engineered to protect encapsulated bacteriophages during gastrointestinal transit and release them specifically in the intestine. In a murine model of *Salmonella Typhimurium*-induced colitis this targeted approach preserved beneficial gut commensals and avoided the severe dysbiosis and diarrhea seen with broad-spectrum antibiotic (ciprofloxacin) therapy [21].

3.3.5. Endodontic infection

One study assessed phage-loaded poloxamer hydrogel in a rat root canal infection model. Treatment by irrigation resulted in reduced bacterial load and decreased periapical inflammation compared with controls [22].

4. Discussion

This systematic review synthesizes the current *in vivo* evidence supporting hydrogel-based local delivery of bacteriophages as a strategy for infection control. Across two clinical case reports, one prospective cohort study and sixteen preclinical animal studies, hydrogel-mediated phage delivery was consistently feasible and was associated with reduced bacterial burden and/or improved tissue healing in the majority of models. Collectively, these findings position hydrogels as enabling platforms for localized phage therapy, while also revealing clear indication-specific performance differences that must be acknowledged when considering clinical translation.

In topical wound/burn models (predominantly rats/mice; one porcine model), phage-hydrogel therapy repeatedly reduced bacterial burden and improved macroscopic and histologic healing. Benefits included faster closure, improved granulation and collagen maturation, reduced inflammation, and—in several burn models—improved survival. By contrast, in deeper orthopedic/implant-associated models, local hydrogel delivery generally yielded partial bacterial reductions (including reductions on implants or surrounding soft tissue) but incomplete eradication was also reported. Non-cutaneous applications, including gastrointestinal and endodontic models, provided proof-of-concept for targeted local phage delivery using hydrogel systems.

4.1. Wound and burn infections

In burn wound models and wound infection models topical phage-hydrogel application resulted in improved wound healing. The therapeutic success in these models derives from several converging factors: (1) direct visual access enabling precise hydrogel placement, (2) high bacterial accessibility within partially hydrated eschar, and (3) rapid phage diffusion through granulation tissue. Notably, Elshamy et al. (2025) demonstrated that carboxymethyl cellulose hydrogels not only delivered phages but also functioned as temporary extracellular matrix scaffolds, promoting dermal collagen fiber maturation through mechanotransduction pathways independent of antimicrobial effects [14]. This dual functionality—antimicrobial plus regenerative—positions hydrogels as active wound healing modulators rather than passive carriers.

4.2. Orthopedic and implant-associated infections

The four preclinical orthopedic studies revealed a more nuanced reality: while bacterial loads on implants and surrounding tissue decreased by 0.5–1.5 $\log_{10}$ CFU, complete eradication of infection was not achieved. Chen et al. (2023) demonstrated that even dual antibiotic-phage delivery via alginate microbeads failed to eradicate *P. aeruginosa* from fracture-related infections, despite achieving therapeutic phage concentrations in soft tissue [17]. Several converging mechanisms plausibly account for the incomplete eradication observed in deep orthopedic and implant-associated models. First, the biofilm extracellular polymeric substance (EPS) matrix acts as both a diffusion barrier and an adsorption sink, binding and sequestering phage particles and reducing the flux of infective phages reaching viable cells; this is consistent with studies showing 10–100-fold slower penetration kinetics for mature biofilms compared to planktonic cultures [29]. Second, the deep-tissue and intra-biofilm microenvironment is frequently hypoxic and nutrient-limited, driving a substantial fraction of the population into slow-growing or dormant persister states; because lytic phages depend on active host transcription and translation to replicate, these metabolically quiescent cells support little or no productive infection and constitute a phage-tolerant reservoir from which infection can rebound. Third, bacterial density within sequestered foci may fall below the proliferation threshold required for self-sustaining phage amplification, so that clearance depends on the delivered (passive, inundative) dose alone. Fourth, host-mediated clearance—including mononuclear phagocyte uptake and the development of neutralizing antibodies—can curtail local phage persistence, as directly observed by Onsea et al., in whose rabbit fracture-related infection model subcutaneous phage delivery was complicated by neutralizing-antibody development and superinfection [20]. Finally, the avascular sanctuary created by necrotic bone and abiotic implant surfaces restricts both phage and immune access to embedded bacteria. Together these factors explain why hydrogel delivery, although it raises and prolongs local phage exposure, may remain insufficient for complete eradication in biofilm-dominated deep infections in the absence of adjunctive surgical debridement and antibiotics. The clinical case by Alt et al. (2024) appears discrepant, reporting successful infection control in a polymicrobial fracture-related infection. However, this apparent success likely reflects the synergistic triad of adequate surgical debridement, systemic antibiotics, and the hydrogel-phage adjunct [10].

4.3. Non-cutaneous applications

The single gastrointestinal study by Yang et al. (2025) represents a paradigm shift in phage delivery logic: pH-responsive oral hydrogel microspheres achieved 2000-fold pathogen reduction in Salmonella colitis while preserving commensal microbiota. This targeted release mechanism, triggered by colonic pH and calcium dissociation from alginate, circumvented the primary obstacle in oral phage therapy—gastric acid inactivation. The avoidance of dysbiosis compared to ciprofloxacin highlights a crucial advantage: phage-hydrogel systems can achieve pathogen-specific editing without collateral microbiome damage, a feat impossible with conventional antibiotics. More broadly, this study also illustrates how stimuli-responsive hydrogels can be engineered to achieve on-demand phage release precisely at the site of infection, responding to environmental cues such as pH, ionic strength, or enzymatic activity [21].

4.4. Importance of sustained and localized phage release

The therapeutic efficacy of bacteriophages is critically dependent on achieving sustained, localized phage–bacteria interactions within the

infected tissue. Phages require physical contact with metabolically active bacterial cells to initiate infection and replication, and their activity is therefore highly sensitive to spatial dilution and temporal fluctuations in local concentration [30]. Hydrogel-based delivery systems can mitigate these limitations by anchoring phages at the site of infection, shielding them from rapid washout, immune clearance, or environmental inactivation, and enabling controlled release over clinically relevant time frames. Sustained local release is particularly important in infections characterized by biofilm formation, heterogeneous bacterial density, or intermittent bacterial replication, where a single bolus of phages may be insufficient to ensure repeated cycles of adsorption and amplification. By maintaining phage presence during critical phases of bacterial regrowth or biofilm disruption, hydrogels may enhance cumulative antibacterial pressure and reduce the likelihood of bacterial persistence [6,31].

4.5. Pharmacokinetic–pharmacodynamic considerations

Defining exposure–response relationships for locally delivered phages requires metrics that differ fundamentally from those used for antibiotics. Classical indices such as the ratio of the area under the concentration–time curve to the minimum inhibitory concentration (AUC/MIC) are not directly transferable, because phages have no MIC and, unlike antibiotics, can self-amplify at the infection site when susceptible host density is sufficient. More appropriate descriptors of local phage pharmacodynamics include the local PFU–time exposure (the magnitude and duration of active phage titre at the infection site), the multiplicity of infection and the instantaneous phage-to-bacterium (PFU/CFU) ratio, and the adsorption rate constant and burst size of the specific phage–host pair, which together determine whether productive ("active," self-sustaining) replication is achieved or whether clearance depends on the delivered ("passive," inundative) dose. The bacterial density threshold for self-sustaining amplification is therefore a key parameter, as are the factors that erode local exposure over time—phage decay and inactivation within the matrix and tissue, mononuclear-phagocyte and antibody-mediated clearance, the emergence of phage-resistant subpopulations, and the proportion of viable phage recoverable from tissue. From a delivery-system perspective, the central rationale for hydrogel encapsulation is precisely to shape these parameters: to sustain local PFU–time exposure above the replication threshold, to protect infectivity, and to prolong residence. Yet only three of the included studies measured tissue phage titres over time, and none reported MOI- or threshold-based exposure metrics. Future studies should report time-resolved local phage titres alongside bacterial density so that delivery systems can be optimised against phage-relevant pharmacodynamic targets rather than empirical dosing [30,33].

4.6. Hydrogel composition and release characteristics

Across all included studies, bacteriophages were delivered locally, and therapeutic success therefore depended primarily on the ability of hydrogels to retain phages at the infection site and enable sustained or controlled release. Despite substantial heterogeneity in hydrogel composition—including alginate-, carboxymethyl cellulose-, chitosan-, Carbopol-, polyvinyl alcohol-, PEG-, poloxamer-, and lipid–hydrogel hybrid systems—no single material class emerged as clearly superior across indications. Instead, broadly comparable outcomes were reported across diverse polymer systems. This convergence suggests that therapeutic performance is driven less by the specific polymer chemistry and more by shared hydrogel physicochemical properties that govern phage release. Parameters such as mesh size and porosity, mechanical stiffness, swelling behaviour, degradation kinetics, and electrostatic interactions are likely to determine phage diffusion, retention, and protection from environmental inactivation. In this context, hydrogels primarily function as local retention and release platforms rather than as material-specific therapeutic agents. This interpretation aligns with broader biomaterials literature indicating that, for antimicrobial delivery, release kinetics and application context often outweigh differences in polymer composition, and that phage–material interactions can be highly phage-specific [31]. At a mechanistic level, the capacity of a hydrogel to retain, protect, and release phages is governed by a small set of physicochemical properties that operate largely independently of the specific polymer chemistry. Network mesh size relative to the hydrodynamic dimensions of the phage (typically ~30–200 nm depending on morphotype and tail length) is a primary determinant of mobility: networks with mesh sizes substantially larger than the virion permit near-free Fickian diffusion and rapid, burst-type release, whereas tighter networks physically constrain diffusion and prolong residence. Degradation kinetics and swelling behaviour modulate this further, because matrix erosion and water uptake progressively enlarge the effective mesh and shift the system from diffusion-controlled toward erosion-controlled release over time. Electrostatic interactions provide a second, tunable handle: most tailed phages carry a net-negative surface charge at physiological pH, so cationic matrices (e.g., chitosan) can transiently immobilise phages and slow release, whereas net-anionic matrices (e.g., alginate, carboxymethyl cellulose) tend to favour release but may afford weaker retention. Finally, the high water content and macromolecular crowding of hydrogels can stabilise phage capsids against desiccation and thermal stress, thereby extending functional half-life *in vivo*, although strongly charged or covalently crosslinked networks (e.g., glutaraldehyde-crosslinked systems) may reduce the recoverable infective titre. These relationships imply that two compositionally distinct hydrogels can produce comparable therapeutic outcomes provided they confer similar mesh size, charge environment, and degradation profile—consistent with the convergent efficacy observed across polymer classes in this review—and they underscore the need for studies that report these parameters explicitly. However, the absence of standardized comparative studies limits definitive conclusions. Direct head-to-head evaluations of hydrogel formulations using identical phages, pathogens, and outcome measures are lacking and represent an important gap for future translational development.

4.7. Translational feasibility

Compassionate use of hydrogel-based phage therapy is rendered feasible through the convergence of three critical factors: (1) the availability of phage preparations that meet quality standards for human application, (2) the magistral preparation regulatory pathway that permits hospital pharmacies to compound phage-hydrogel products on-demand under national regulations, and (3) the procedural integration of phage therapy into established clincal workflows without disrupting operative time or requiring specialized infrastructure [32]. It should be emphasized that the available clinical evidence comprises two single compassionate-use/salvage case reports and one small prospective cohort, all uncontrolled and corresponding to Level IV evidence in conventional hierarchies. These reports establish feasibility and provide preliminary safety signals but do not permit conclusions regarding clinical efficacy.

4.8. Limitations

Several limitations should be considered when interpreting the findings of this systematic review. First, although the included studies collectively provide consistent direction-of-effect evidence, the substantial methodological heterogeneity across models limits cross-study comparability. Infection indications, animal species, bacterial strains, phage selection, hydrogel formulations, and outcome measures varied widely, precluding quantitative meta-analysis and preventing direct comparison of effect sizes. Phage-loaded hydrogels were administered topically, intraoperatively, by local injection, irrigation, or orally, often using indication-specific rationales. Only one study systematically compared different routes within the same infection model, making it

difficult to define optimal delivery strategies for specific indication [20]. Furthermore, only three studies measured tissue phage concentrations over time, and none reported phage-relevant exposure metrics (e.g., local PFU–time exposure, multiplicity of infection, or the bacterial density threshold for amplification; see *Pharmacokinetic–pharmacodynamic considerations*) capable of linking delivery to efficacy. In their absence, dose and formulation selection remain largely empirical.

4.9. Recommendations for future studies

To enable cross-study comparison and accelerate translation, future *in vivo* investigations should converge on a set of minimum design and reporting standards. (i) Model selection: use defined, reported inocula and clinically relevant pathogens and strains, and explicitly distinguish acute from biofilm-associated infection, since efficacy differs markedly between these states. (ii) Phage dosing: report absolute titre (PFU) and, where bacterial load is known, multiplicity of infection, together with the number and timing of doses; measure time-resolved local phage titres wherever feasible. (iii) Hydrogel formulation: characterise the matrix beyond composition to include mesh size or equivalent crosslink density, rheological/mechanical properties, swelling and degradation behaviour, and *in vitro* release kinetics, ideally complemented by *in vivo* retention data. (iv) Comparator arms: include defined controls—free (non-encapsulated) phage, blank hydrogel, antibiotic-loaded hydrogel, systemic antibiotic, and/or untreated animals—so that the contributions of the phage, the matrix, and any co-interventions can be disentangled. (v) Efficacy endpoints: harmonise around quantitative bacterial burden (CFU) at predefined timepoints, with biofilm-specific quantification on implants where relevant, alongside standardized healing and histological metrics. (vi) Safety and immunogenicity: report local tolerance, neutralizing-antibody development, and adequate follow-up duration. Adoption of these standards—ideally within head-to-head studies using identical phage–pathogen pairs across formulations—would allow the field to move from demonstrating feasibility toward defining optimal, indication-specific delivery and dosing regimens.

5. Conclusion

This systematic review demonstrates that hydrogel-based local delivery of bacteriophages is a feasible strategy for infection control, with consistent *in vivo* evidence supporting reductions in bacterial burden and improvements in tissue healing. Therapeutic efficacy was most robust in superficial wound and burn infections, where localized and sustained phage–bacteria interactions can be reliably achieved, while deep orthopedic and implant-associated infections showed more limited, albeit biologically meaningful, effects. Hydrogel-based local bacteriophage delivery may be reasonably considered in carefully selected cases with localized, difficult-to-treat infections.

CRediT authorship contribution statement

Nike Walter: Writing – original draft, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Christoph Brochhausen:** Writing – review & editing, Methodology. **Thaqif El Khassawna:** Writing – review & editing, Validation. **Corina Vater:** Writing – review & editing. **Aaron Teja Bolte:** Writing – original draft, Visualization, Methodology, Investigation, Data curation, Conceptualization. **Mohammadali Khan Mirzaei:** Writing – review & editing, Validation. **Ronald Man Yeung Wong:** Writing – review & editing, Validation. **Wing-Hoi Cheung:** Writing – review & editing. **Christian Heiss:** Writing – review & editing, Methodology. **Volker Alt:** Writing – review & editing. **Anja Lode:** Writing – review & editing, Validation, Project administration. **Li Deng:** Writing – review & editing, Project administration, Methodology. **Markus Rupp:** Writing – review & editing, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization.

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Declaration of competing interest

The authors have no conflict of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jconrel.2026.115335.

Data availability

The data underlying this study are available upon request from the corresponding author.

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