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Systematic review

PERSONALIZED PHAGE THERAPY FOR DRUG-RESISTANT AND DIFFICULT-TO-TREAT BACTERIAL INFECTIONS: A SYSTEMATIC REVIEW OF HUMAN CLINICAL EVIDENCE AND NARRATIVE SYNTHESIS

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ABSTRACT

Background: Personalized bacteriophage therapy is a precision-oriented strategy for drug-resistant and otherwise difficult-to-treat bacterial infections. Its defining feature is the selection, adaptation, or engineering of a phage preparation against the patient clinical isolate. This biological specificity may improve target engagement, but it also complicates standardization, causal inference, and conventional fixed-product trial design.

Objective: To systematically evaluate human clinical evidence on personalized or strain-matched phage therapy and to distinguish direct personalized evidence from indirect randomized evidence generated with fixed phage preparations.

Methods: The review was structured according to PRISMA 2020. PubMed/MEDLINE, Embase, Scopus, Web of Science Core Collection, Cochrane CENTRAL, ClinicalTrials.gov, and citation sources were searched through 8 July 2026. Eligible primary studies administered bacteriophages to patients with multidrug-resistant, extensively drug-resistant, pan-drug-resistant, or otherwise difficult-to-treat bacterial infections. Direct evidence required patient-isolate matching or individualized phage selection, adaptation, or engineering. Fixed-product randomized trials were retained as indirect evidence. Two reviewers independently screened reports and extracted data. RoB 2 was used for randomized trials, while JBI case-series or case-report domains were used for uncontrolled personalized studies. Findings were synthesized narratively because of marked clinical and methodological heterogeneity.

Results: The search identified 468 records; 346 remained after removal of 122 duplicates, 43 full-text reports were assessed, and 13 reports representing 10 study datasets were included. These comprised four personalized cohorts or case series, three independent case-level or mechanistic studies, three linked secondary case reports retained for additional detail, and three randomized trials of fixed phage preparations. The largest personalized series reported clinical improvement in 88 of 114 treated infection episodes (77.2%) and target-pathogen eradication in 65 of 106 episodes with microbiological follow-up (61.3%). A 12-case expanded-access series reported bacterial eradication in 5 of 12 cases and clinical improvement in 7 of 12, while a 10-case intravenous series reported successful outcomes in 7 of 10 patients. In nine adults with cystic fibrosis and multidrug-resistant or pan-drug-resistant Pseudomonas aeruginosa, personalized inhaled therapy was associated with an approximately 10^4 CFU/mL median reduction in sputum bacterial burden and a 6-percentage-point median short-term increase in ppFEV1. Certainty remained very low for effectiveness because the direct evidence was uncontrolled, heterogeneous, and vulnerable to confounding, report overlap, and selective publication.

Conclusions: Personalized phage therapy has a strong mechanistic rationale and repeated clinical signals in selected rescue settings, but current evidence does not establish a causal average treatment effect. The most defensible clinical model is adjunctive precision infectious-disease care combining a matched, quality-controlled phage preparation with optimized antibacterial therapy, source control, and longitudinal microbiological monitoring.

Keywords: bacteriophage therapy; personalized phage therapy; antimicrobial resistance; multidrug resistance; extensively drug-resistant infection; phage susceptibility testing; phage-antibiotic interaction; antiphage immunity; PRISMA 2020.

1. Introduction

Antimicrobial resistance (AMR) reduces the reliability of routine and high-complexity medical care. A global analysis estimated that bacterial AMR was directly responsible for 1.27 million deaths and associated with 4.95 million deaths in 2019 [1]. The World Health Organization identifies AMR as a major public health threat because resistance increases the probability of treatment failure in surgery, transplantation, cancer therapy, intensive care, and other settings that depend on effective antibacterial treatment [2]. In the European Union and European Economic Area, antimicrobial-resistant bacterial infections have been estimated to cause more than 35,000 deaths annually [3].

Bacteriophages provide an antibacterial mechanism that differs fundamentally from conventional antibiotics. They infect susceptible bacteria, replicate within the host cell, and may remain active against organisms resistant to multiple antibiotic classes. Therapeutic phages are not interchangeable agents, however. Host range is usually narrow; susceptibility can differ between closely related isolates; and activity can be modified by receptor expression, biofilm structure, phage pharmacokinetics, concomitant antibiotics, bacterial resistance, and host immune neutralization.

Personalized or strain-matched phage therapy therefore represents the most biologically coherent form of clinical phage treatment. In this model, a phage or defined cocktail is selected, adapted, or engineered against the patient isolate and incorporated into a broader treatment plan. The approach is particularly relevant to chronic airway infection,

prosthetic or biofilm-associated infection, bloodstream infection, osteoarticular infection, and rescue therapy when conventional options are limited.

Recent human evidence demonstrates both promise and uncertainty. A multinational analysis of 100 consecutive patients reported clinical and microbiological improvement across heterogeneous difficult-to-treat infections [4]. A focused cohort of adults with cystic fibrosis suggested that personalized inhaled phages may reduce Pseudomonas aeruginosa burden and improve short-term lung function [5]. Expanded-access series have also shown that individualized production pathways can be implemented across multiple pathogens and infection sites [6,7]. Conversely, mechanistic failure analysis has implicated pre-existing antiphage antibodies and bacterial heteroresistance in loss of treatment activity [8]. These findings indicate that outcome depends not only on in vitro lysis, but on the full patient-pathogen-phage-antibiotic system.

This review was therefore designed to evaluate human clinical evidence supporting personalized phage therapy, distinguish it from fixed-product randomized trials, and identify the minimum methodological elements required for reproducible assessment. Reporting was structured according to the PRISMA 2020 statement [9].

2. Objective and Review Questions

The objective was to evaluate human clinical evidence on personalized or strain-matched bacteriophage therapy for drug-resistant or otherwise difficult-to-treat bacterial infections and to determine how study design, phage matching, concomitant therapy, resistance, and host immunity influence interpretation.

- What human clinical evidence supports personalized or strain-matched bacteriophage therapy?
- Which clinical, microbiological, functional, and safety outcomes have been reported?
- How should randomized trials of fixed phage preparations be interpreted in relation to personalized treatment?
- How do phage susceptibility, phage-antibiotic interactions, resistance, heteroresistance, and antiphage immunity influence treatment response?
- Which study designs can preserve patient-isolate matching while improving causal inference?

3. Methods

3.1. Reporting Standard and Protocol Status

The review was prepared in accordance with PRISMA 2020 [9]. The protocol was not prospectively registered. This limitation reduces confidence that all eligibility and analytical decisions were finalized before inspection of the evidence and is explicitly considered in the interpretation of the review.

3.2. Eligibility Criteria

Eligibility criteria were structured to separate direct personalized evidence from indirect randomized evidence. Reviews, consensus documents, and methodological proposals were used only as contextual sources and were not counted as included clinical studies.

Table 1. Review framework and eligibility criteria

Element	Definition
Population	Patients of any age with MDR, XDR, PDR, or otherwise difficult-to-treat bacterial infection, including airway, bloodstream, wound, urinary, device-associated, osteoarticular, intra-abdominal, and disseminated infection.
Direct intervention	Bacteriophage therapy selected, adapted, or engineered against the patient clinical isolate, administered alone or with antibiotics by intravenous, inhaled, oral, topical, intracavitary, intravesical, or other clinically relevant routes.
Indirect intervention	Fixed phage cocktails or standardized products evaluated in randomized or controlled trials without mandatory individual isolate matching. These studies were retained only for indirect evidence on safety, feasibility, formulation, dosing, and trial design.
Comparators	Placebo, standard antibacterial therapy, an active control, historical control, before-after comparison, or no comparator in compassionate-use cohorts and case reports.
Primary outcomes	Clinical improvement or cure; all-cause mortality; microbiological eradication or clearance; bacterial-load reduction; organ-specific functional outcomes; and serious or treatment-related adverse events.
Secondary outcomes	Phage resistance or heteroresistance; phage-antibiotic interactions; antiphage neutralization; feasibility; turnaround time; and treatment modification.
Study designs	Randomized trials, non-randomized comparative studies, prospective or retrospective cohorts, case series, and clinically informative case reports.
Exclusions	In vitro-only and animal-only studies; reviews without original patient data; editorials; protocols without results; environmental or agricultural applications; non-therapeutic phage studies; and reports without relevant clinical outcomes.

Table 1 operationalizes the scope of the review by distinguishing direct isolate-matched treatment from fixed-product interventions. The framework deliberately permits broad clinical populations and administration routes, but it requires patient-specific phage selection, adaptation, or engineering for classification as direct personalized evidence. It also separates patient-centered effectiveness and safety outcomes from mechanistic and treatment-process outcomes used to explain response or failure.

3.3. Definition of Personalized Phage Therapy

A clinical report was classified as personalized when the therapeutic preparation was chosen on the basis of testing against the patient isolate, or when phages were adapted or engineered for that isolate. Reports using a fixed product without mandatory isolate matching were classified as indirect evidence, even when the target pathogen was specified. MDR, XDR, and PDR classifications were accepted as reported by the primary authors. When a report used the broader term difficult-to-treat without a formal resistance category, eligibility required documented failure, intolerance, or absence of reasonable conventional antibacterial options.

3.4. Information Sources and Search Strategy

PubMed/MEDLINE, Embase, Scopus, Web of Science Core Collection, Cochrane CENTRAL, ClinicalTrials.gov, and citation sources were searched from database inception through 8 July 2026. Database-specific strategies are provided in Appendix 1. Backward and forward citation searching was performed for included clinical reports and relevant reviews. The searches identified 428 records from bibliographic databases, 23 from trial registers, and 17 through citation searching or other methods.

3.5. Study Selection and Record Management

Two reviewers independently screened titles and abstracts and then assessed full-text reports. Disagreements were resolved by consensus and, when required, consultation with a third reviewer. One primary reason for exclusion was assigned to each excluded full-text report using the following hierarchy: wrong population or intervention; in vitro or animal evidence only; review, editorial, protocol, consensus, or methodological publication without eligible primary clinical data; no extractable relevant outcome; and duplicate or overlapping report without additional data. Multiple publications describing the same cohort were linked and treated as reports of one study. The most complete peer-reviewed publication was designated as the primary report. Earlier or more detailed case reports were retained only when they contributed clinically or mechanistically relevant information, and their participants and outcomes were not counted independently. Possible, but unconfirmed, overlap was flagged and numerical outcomes were not summed across the potentially overlapping reports.

3.6. Data Extraction

A structured form was used to extract study design, country, clinical setting, infection site, pathogen, resistance profile, sample size, phage-selection procedure, phage susceptibility method, formulation, dose, route, concomitant antibiotics, source-control procedures, comparator, follow-up, clinical and microbiological outcomes, adverse events, emergence of resistance or heteroresistance, antiphage immunity, funding, and conflicts of interest. Data extraction was performed independently by two reviewers and reconciled by consensus.

3.7. Risk of Bias

Randomized trials were assessed with RoB 2 at the outcome level [10]. Non-randomized comparative studies, if identified, were to be assessed with ROBINS-I [11]. Uncontrolled cohorts and case series were evaluated using JBI case-series domains [12], and individual case reports were evaluated using JBI case-report domains [13]. Because JBI tools do not generate a standardized numeric total or a universal overall category, the review reports domain-based methodological limitations rather than an artificial score. Case reports were not used to estimate average effectiveness.

3.8. Certainty of Evidence

Certainty was evaluated by outcome using GRADE domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias [14]. Randomized trials of fixed products were downgraded for indirectness when

used to interpret personalized therapy. Mechanistic findings such as PAS, resistance, heteroresistance, and antiphage neutralization were summarized separately and were not combined into a single GRADE outcome.

3.9. Synthesis and Unit of Analysis

Meta-analysis was not performed because of substantial heterogeneity in population, infection site, pathogen, phage product, matching procedure, route, dose, antibiotic co-therapy, source control, follow-up, and outcome definition. A structured narrative synthesis was undertaken across four evidence layers: personalized cohorts or case series, independent case-level or mechanistic studies, linked secondary case reports retained for additional detail, and indirect randomized evidence from fixed products. The unit of analysis was the study dataset rather than the publication. When a study reported infection episodes rather than patients, the original denominator was retained and explicitly identified.

4. Results

4.1. Study Selection

The searches identified 468 records: 428 from bibliographic databases, 23 from trial registers, and 17 through citation searching or other methods. After removal of 122 duplicate records, 346 titles and abstracts were screened, of which 301 were excluded. Forty-five full-text reports were sought for retrieval; two reports could not be obtained, leaving 43 reports for full-text assessment. Thirty reports were excluded: nine evaluated the wrong population or intervention, seven contained only in vitro or animal evidence, eight were reviews, editorials, protocols, consensus documents, or methodological publications without eligible primary clinical data, four did not report an extractable relevant clinical outcome, and two were duplicate or overlapping reports without additional data. Thirteen reports were retained and represented ten study datasets.

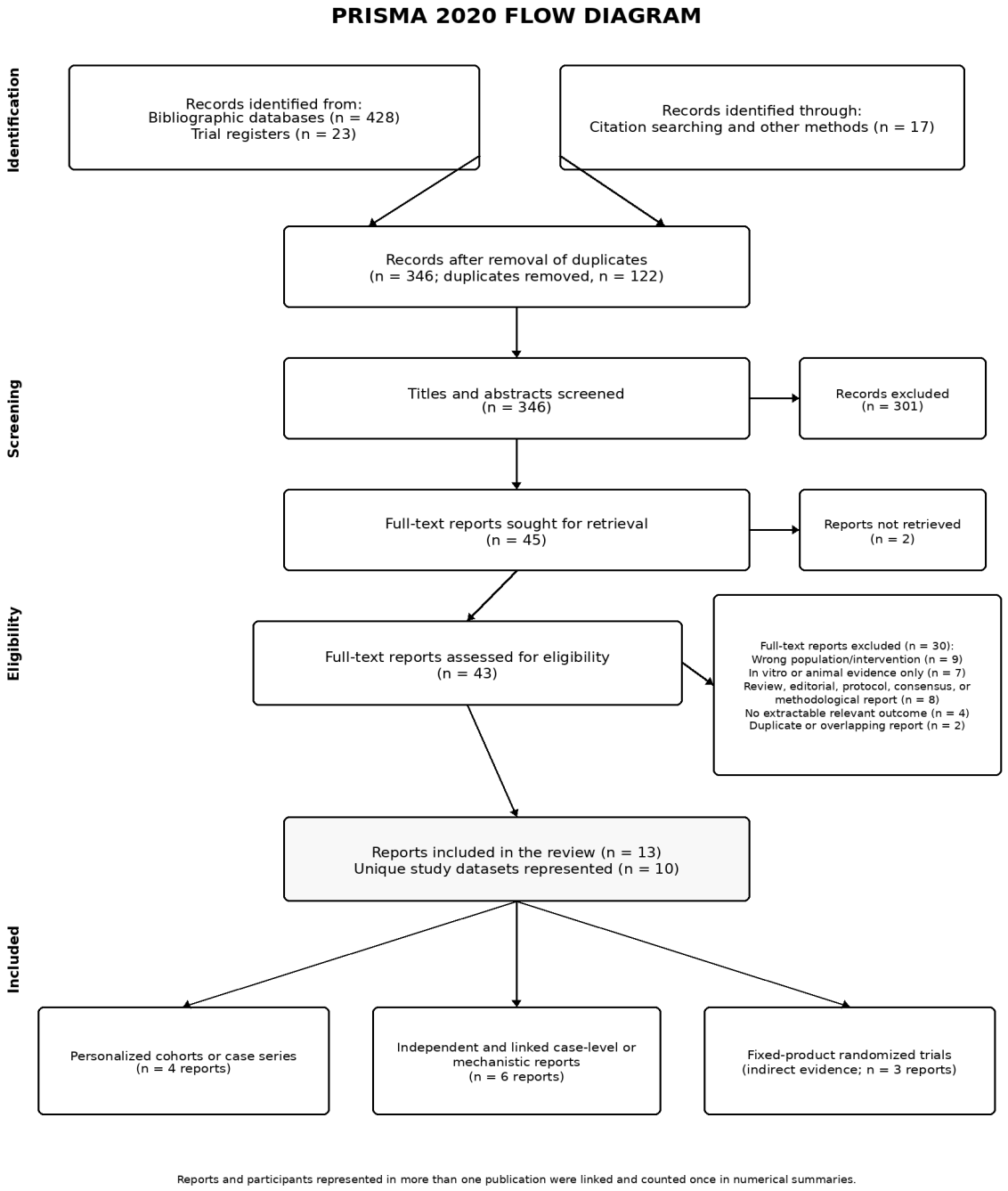

Figure 1. PRISMA 2020 flow diagram.

4.2. Characteristics of Included Clinical Evidence

The synthesis included 13 clinical reports representing 10 study datasets. Four reports were primary personalized cohorts or case series, three were independent case-level or mechanistic studies, three were linked secondary case reports retained for additional clinical or mechanistic detail, and three were randomized trials of fixed phage preparations used as indirect evidence. The principal characteristics and contribution of each report are summarized in Table 2.

Table 2. Characteristics and contribution of included clinical reports

Report	Design and population	Intervention	Main findings	Principal limitations	Role/overlap
Pirnay et al., 2024 [4]	Retrospective multinational series; 100 patients, 114 infection episodes	Individual isolate-matched phages or cocktails; antibiotics in most episodes	Clinical improvement 88/114; eradication 65/106; PAS 9/10 tested; resistance 7/16 evaluated	Largest consecutive personalized dataset; uncontrolled, heterogeneous, variable follow-up	Primary multinational cohort; includes cases previously reported by Ferry et al. and Van Nieuwenhuyse et al.

Report	Design and population	Intervention	Main findings	Principal limitations	Role/overlap
Chan et al., 2025 [5]	Compassionate-use cohort; 9 adults with cystic fibrosis and MDR/PDR P. aeruginosa	Personalized nebulized phage or cocktail selected to exploit receptor-associated trade-offs	Approximate median sputum reduction 10^4 CFU/mL; median ppFEV1 increase 6 percentage points; no treatment-related adverse events reported	Small, uncontrolled, short follow-up, concurrent or recent antibiotics	Primary focused cohort; final peer-reviewed report used as the study source.
Green et al., 2023 [6]	Retrospective expanded-access series; 12 customized-treatment cases	Patient-specific phage production and treatment across multiple infection types	Bacterial eradication 5/12; clinical improvement 7/12; favorable clinical or microbiological outcome in two-thirds; no significant treatment-related toxicity reported	No comparator, heterogeneous indications, selective referral	Primary expanded-access series; possible partial overlap with Aslam et al. for one case.
Aslam et al., 2020 [7]	Single-center retrospective series; first 10 consecutive intravenous cases	Individualized intravenous phage therapy for MDR infections	Successful outcome in 7/10 cases; practical data on timing, regulation, and administration	Small uncontrolled series, major co-interventions	Primary single-center series; includes the patient described by Schooley et al.
Gordillo Altamirano et al., 2026 [8]	Mechanistic failure report; patient with cystic fibrosis and severe Bordetella infection	Compassionate-use personalized therapy	Pre-existing cross-reactive antiphage antibodies and bacterial heteroresistance implicated in failure	Single selected failure; not an effect estimate	Independent mechanistic failure study.
Schooley et al., 2017 [15]	Case report; disseminated MDR A. baumannii infection	Personalized phage cocktails plus antibiotics	Clinical rescue signal; resistance and phage-antibiotic interactions were clinically relevant	Single rescue case, multiple co-interventions	Linked secondary case report nested within Aslam et al.; not counted independently in numerical summaries.
Dedrick et al., 2019 [16]	Case report; disseminated drug-resistant M. abscessus infection	Engineered phage combination	Clinical and microbiological improvement reported	Single highly selected case; engineered intervention	Independent case-level feasibility study in the current evidence set.
Ferry et al., 2022 [17]	Case report; PDR P. aeruginosa spinal abscess	Personalized local and intravenous phages plus surgery and antibiotics	Clinical healing despite bacterial persistence during part of the course	Single case, extensive source control and antibiotics	Linked secondary case report nested within Pirnay et al.; retained for detailed clinical and microbiological information.
Köhler et al., 2023 [18]	Case report; chronic MDR P. aeruginosa lung infection	Repeated personalized aerosolized phage treatment	Favorable clinical course with isolate-directed iterative treatment	Single case and repeated co-interventions	Independent case-level airway study.
Van Nieuwenhuyse et al., 2022 [19]	Case report; toddler with XDR P. aeruginosa sepsis after liver transplantation	Intravenous phage-antibiotic combination for 86 days	Clinical and microbiological improvement permitting retransplantation; no antibody-mediated neutralization reported	Single pediatric rescue case	Linked secondary case report nested within Pirnay et al.; retained for pediatric and immunological detail.
Jault et al., 2019 [20]	Randomized double-blind phase I/II trial in P. aeruginosa burn-wound infection	Fixed low-concentration cocktail, not individually matched	Expected efficacy not demonstrated; delivered titer and formulation were important	Serious indirectness for personalized therapy	Independent indirect randomized study.
Leitner et al., 2021 [21]	Randomized placebo-controlled double-blind trial in UTI after transurethral prostate resection	Fixed intravesical preparation	Controlled safety and feasibility data; no direct personalized-treatment estimate	Intervention did not require individual matching	Independent indirect randomized study.
Sarker et al., 2016 [22]	Randomized trial in children with acute E. coli diarrhea	Two fixed oral coliphage preparations	No clear clinical benefit established	Target abundance, ecological niche, and host matching limited interpretation	Independent indirect randomized study.

Table 2 shows that the numerical evidence is concentrated in four uncontrolled personalized cohorts or case series, whereas the remaining personalized reports primarily contribute detailed information on feasibility, resistance, immune neutralization, and clinical decision-making. The three randomized trials provide more controlled safety and implementation data, but their fixed preparations do not directly test whether isolate-specific matching improves patient outcomes.

4.3. Assessment of Publication and Participant Overlap

Thirteen included reports represented ten study datasets. Three detailed case reports described patients who were subsequently incorporated into larger series. Schooley et al. [15] was linked to the Aslam et al. series [7], while Ferry et al. [17] and Van Nieuwenhuyse et al. [19] were linked to the multinational Pirnay et al. series [4]. These reports were retained because they provided additional clinical, microbiological, pharmacological, or mechanistic detail, but their patients and outcomes were not counted independently. Possible partial overlap was also identified between Green et al. [6] and Aslam et al. [7] for one liver-transplant recipient with recurrent MDR Escherichia coli urinary infection. Because an explicit patient-level linkage was unavailable, this relationship was

classified as possible rather than confirmed, and outcomes were not summed across the two series.

Table 3. Report-to-study overlap assessment

Primary report	Linked report	Classification	Treatment in synthesis
Aslam et al., 2020 [7]	Schooley et al., 2017 [15]	Confirmed nested patient	Aslam used for series-level outcomes; Schooley retained only for detailed mechanism and clinical course.
Pirnay et al., 2024 [4]	Ferry et al., 2022 [17]	Confirmed nested case	Pirnay used for cohort outcomes; Ferry retained for detailed management of PDR spinal infection.
Pirnay et al., 2024 [4]	Van Nieuwenhuyse et al., 2022 [19]	Confirmed nested case	Pirnay used for cohort outcomes; Van Nieuwenhuyse retained for pediatric, transplant, and neutralization detail.
Green et al., 2023 [6]	Aslam et al., 2020 [7]	Possible partial overlap	No cross-series pooling; the potentially shared case was not counted twice in combined narrative totals.

As summarized in Table 3, report-level inclusion did not imply that every publication represented an independent patient dataset. Linked reports were retained only when they added clinically relevant detail, while cohort-level outcomes were taken from the designated primary publication. This approach prevented double counting and preserved the distinction between the number of included reports and the number of unique studies.

4.4. Direct Evidence from Personalized Cohorts and Case Series

The strongest direct numerical evidence was the multinational series reported by Pirnay et al. [4]. The unit of analysis was the treated infection episode. Clinical improvement occurred in 88 of 114 episodes (77.2%), and eradication of the target organism was documented in 65 of 106 episodes with microbiological follow-up (61.3%). These results provide a clinically relevant signal across severe and heterogeneous infections, but they do not establish a counterfactual outcome because the study had no concurrent control group and most patients received antibiotics, source control, or other interventions.

Green et al. reported 12 expanded-access cases managed through a customized production pipeline [6]. Bacterial eradication was reported in 5 of 12 cases and clinical improvement in 7 of 12; overall, two-thirds had a favorable clinical or microbiological outcome. The series demonstrates feasibility across pathogens and clinical settings, but outcome definitions and follow-up differed between patients.

Aslam et al. described the first 10 consecutive intravenous phage-therapy cases at a single United States center [7]. Successful outcomes were reported in 7 of 10 cases. The report is particularly informative regarding referral, regulatory procedures, product acquisition, timing, and administration, but its small size and extensive co-interventions preclude causal estimation.

The cystic fibrosis cohort reported by Chan et al. [5] provides a more clinically focused estimate. Nine adults received personalized inhaled phage therapy directed against MDR/PDR P. aeruginosa. The median sputum bacterial-load reduction was approximately 10^4 CFU/mL during short-term follow-up, and the median increase in ppFEV1 was 6 percentage points. The temporal pattern is biologically coherent, but the sample was small and uncontrolled, and concurrent or recent antibiotic exposure limits attribution.

4.5. Case-Level and Mechanistic Evidence

Independent case-level studies demonstrate operational feasibility in drug-resistant M. abscessus infection treated with engineered phages [16] and chronic MDR P. aeruginosa airway infection treated with repeated isolate-directed aerosolized phages [18]. Linked secondary reports provide additional detail on disseminated A. baumannii infection [15], PDR P. aeruginosa spinal infection [17], and XDR P. aeruginosa sepsis after liver transplantation [19], but these patients were not counted independently because they were nested within larger series.

The failure report by Gordillo Altamirano et al. [8] is methodologically valuable because it describes an unsuccessful course rather than a selected clinical success. Pre-existing cross-reactive antiphage antibodies and bacterial heteroresistance were implicated in treatment failure, illustrating that in vitro susceptibility at a single time point may not predict adequate in vivo exposure or durable population-level bacterial susceptibility.

4.6. Indirect Evidence from Fixed-Product Randomized Trials

Three randomized trials were retained as indirect evidence because they evaluated fixed products rather than treatment selected against the patient isolate [20-22]. PhagoBurn demonstrated that inadequate delivered titer, product instability, and non-personalized formulation can obscure a clinical effect even in a biologically plausible indication [20]. The intravesical urinary-tract trial showed that controlled administration is feasible, but it did not test whether isolate-specific matching improves outcome [21]. The pediatric diarrhea trial did not establish clear benefit and highlighted the importance of target abundance, ecological niche, and effective host coverage [22]. These trials were therefore interpreted primarily as evidence about formulation, exposure, safety, and trial design rather than direct tests of personalized therapy.

4.7. Microbiological and Treatment-Process Determinants

- Phage susceptibility testing: a spot test alone may overestimate activity because clearing can result from lysis from without or high local phage concentration. Plaque-based testing, efficiency of plating, and liquid growth kinetics provide complementary information [23,24].

- Phage-antibiotic interactions: PAS was observed in 9 of 10 tested cases in the Pirnay series [4]. This small and selected denominator should be interpreted as a process signal rather than proof of universal synergy.
- Phage resistance: resistance emerged in 7 of 16 evaluated cases in the Pirnay series [4]. Resistance can sometimes impose a fitness cost or restore antibiotic susceptibility, but this requires isolate-specific validation [25].
- Bacterial heteroresistance: pre-existing subpopulations with reduced phage susceptibility can permit persistence despite apparent activity in standard assays [8].
- Antiphage immunity: pre-existing or treatment-induced neutralizing antibodies may be relevant in chronic infection, repeated courses, and systemic administration [8].
- Source control and concomitant therapy: drainage, debridement, device removal, and active antibiotics remain integral components of care and major confounders of observed outcome.

4.8. Safety

Short-term tolerability was generally acceptable. In the 100-patient series, seven suspected non-serious adverse reactions were reported and resolved [4]. No treatment-related adverse events were reported in the nine-patient inhaled cystic fibrosis cohort [5], and the 12-case expanded-access series did not identify significant treatment-related toxicity [6]. A previous systematic review similarly found that serious toxicity attributable to phages was uncommon, although adverse-event ascertainment was inconsistent and follow-up was usually short [26].

Safety interpretation must remain route-specific. For systemic administration, sterility, endotoxin burden, residual host-cell material, infusion reactions, cytokine responses, and immune neutralization require explicit monitoring. Absence of reported toxicity in compassionate-use reports should not be equated with definitive safety because outcome ascertainment was rarely standardized.

4.9. Certainty of Evidence

Certainty was evaluated at the outcome level using the GRADE domains of risk of bias, inconsistency, indirectness, imprecision, and publication bias. Because no randomized trial directly evaluated isolate-matched personalized therapy, evidence for clinical improvement, microbiological response, and functional outcomes was derived predominantly from uncontrolled observational reports. These outcomes therefore began at a low level of certainty and were further downgraded when small samples, heterogeneous definitions, co-interventions, potential publication overlap, or selective reporting materially limited interpretation.

Table 4. Summary of findings and certainty of evidence

Outcome	Observed evidence	Certainty	Rationale
Clinical improvement	88/114 episodes in the largest series; 7/10 successful outcomes in one intravenous series; 7/12 improved in an expanded-access series	Very low	Uncontrolled designs, co-interventions, heterogeneous definitions, potential overlap, and probable publication bias.
Microbiological eradication	65/106 episodes in the largest series; 5/12 cases in an expanded-access series	Very low	Variable sampling, timing, infection sites, and definitions; no randomized personalized comparison.
Bacterial-load reduction in cystic fibrosis	Approximate median reduction of 10^4 CFU/mL in 9 adults	Very low	Small uncontrolled cohort, short follow-up, concurrent or recent antibiotics.
Lung function in cystic fibrosis	Median ppFEV1 increase of 6 percentage points	Very low	No comparator, imprecision, regression to the mean, and uncertain attribution.
Short-term safety	Mostly non-serious reactions in personalized series; randomized fixed-product trials provide additional indirect safety data	Low	Inconsistent ascertainment, short follow-up, route heterogeneity, and indirectness of fixed-product trials.

Table 4 indicates that all effectiveness outcomes remain supported by very-low-certainty evidence. The direction of findings is generally favorable, but causal attribution is limited by uncontrolled designs, imprecision, heterogeneous outcome definitions, concomitant antibiotics and source-control procedures, and probable selective publication. Short-term safety was rated as low certainty rather than very low because serious treatment-related toxicity was uncommon across several clinical settings and was supported by indirect randomized evidence; nevertheless, route-specific and long-term safety remain insufficiently characterized.

4.10. Risk of Bias

Methodological appraisal was matched to study design. RoB 2 was applied to randomized trials, while JBI case-series and case-report domains were used for uncontrolled personalized studies. Case reports were assessed for completeness and internal coherence but were not treated as sources of comparative effect estimates. For randomized fixed-product trials, risk of bias was considered separately from applicability: a trial could have stronger internal validity while remaining indirect for the isolate-matched intervention addressed by this review.

Table 5. Study-level methodological assessment and principal limitations

Study	Tool	Interpretation	Main basis
Pirnay et al., 2024 [4]	JBI case-series domains	Major methodological limitations	Uncontrolled compassionate-use treatment, confounding by antibiotics and source control, heterogeneous outcomes, and variable follow-up.
Chan et al., 2025 [5]	JBI case-series domains	Major methodological limitations	Small sample, no comparator, short follow-up, and concurrent or recent antibiotics.

Study	Tool	Interpretation	Main basis
Green et al., 2023 [6]	JBI case-series domains	Major methodological limitations	Selective referral, heterogeneous indications and outcomes, no comparator.
Aslam et al., 2020 [7]	JBI case-series domains	Major methodological limitations	Small single-center series, extensive co-interventions, and non-standardized outcomes.
Gordillo Altamirano et al., 2026 [8]	JBI case-report domains	Not suitable for effect estimation	Single selected failure case; high mechanistic value but no average effect estimate.
Schooley et al., 2017 [15]	JBI case-report domains	Not independently counted for effect estimation	Single rescue case and multiple co-interventions.
Dedrick et al., 2019 [16]	JBI case-report domains	Not suitable for effect estimation	Single highly selected case and engineered intervention.
Ferry et al., 2022 [17]	JBI case-report domains	Not independently counted for effect estimation	Single case with surgery and multiple antibacterial interventions.
Köhler et al., 2023 [18]	JBI case-report domains	Not suitable for effect estimation	Single case, repeated treatments, and time-varying co-interventions.
Van Nieuwenhuyse et al., 2022 [19]	JBI case-report domains	Not independently counted for effect estimation	Single pediatric rescue case with intensive multidisciplinary care.
Jault et al., 2019 [20]	RoB 2	Some concerns	Randomized design, but delivered phage concentration and intervention fidelity complicated interpretation.
Leitner et al., 2021 [21]	RoB 2	Some concerns	Controlled design with residual concerns regarding intervention fidelity and applicability.
Sarker et al., 2016 [22]	RoB 2	Some concerns	Randomized design, but host matching and effective ecological exposure limited interpretation.

Table 5 demonstrates that no direct personalized study provided a low-risk comparative estimate of treatment effect. The recurring limitations were absence of a concurrent comparator, confounding by antibiotics and source control, selective access to compassionate-use treatment, non-standardized outcome assessment, and variable follow-up. Linked case reports were not counted independently for effectiveness. The randomized fixed-product trials were judged to have some concerns, mainly because intervention fidelity, delivered phage exposure, host matching, or ecological target availability complicated interpretation.

5. Discussion

This review identifies a coherent but low-certainty pattern. Personalized phage therapy is technically feasible and has produced repeated clinical and microbiological signals in selected patients with severe drug-resistant infections. The strongest numerical evidence comes from uncontrolled multinational and expanded-access series rather than randomized personalized comparisons. The certainty of an efficacy estimate therefore remains very low, even when the observed proportions of clinical improvement or microbiological response appear substantial.

The distinction between personalized therapy and fixed-product randomized trials is central. Randomization strengthens internal validity only when the tested intervention adequately represents the clinical strategy of interest. A fixed preparation with incomplete host coverage, inadequate delivered titer, or unstable formulation cannot directly answer whether a correctly matched phage is effective against a susceptible patient isolate. Conversely, an uncontrolled personalized case cannot determine how much improvement was caused by the phage rather than antibiotics, surgery, drainage, device removal, natural recovery, or selective reporting. The evidence layers are complementary, but they answer different questions.

The review also shows that personalization is not equivalent to observing a clear zone on agar. A reproducible clinical pathway requires strain-level bacterial identification, complementary susceptibility methods, explicit assessment of the antibiotics retained in the regimen, predefined microbiological sampling, and repeat testing when cultures remain positive. In chronic or repeatedly treated patients, neutralizing activity may alter systemic or local exposure even when the phage remains active in vitro.

Phage-antibiotic interaction is promising but should be described cautiously. The high proportion of PAS among tested cases in the multinational series is notable [4], but the denominator was small and testing was selective. PAS should therefore be prospectively incorporated when feasible, particularly when phages are intended as adjuncts to a predefined antibiotic regimen, rather than presented as a proven universal modifier of response.

Resistance should be incorporated into protocol design rather than treated as an unexpected event. Because phages and bacteria co-evolve, resistant or heteroresistant subpopulations may emerge rapidly. The clinical consequence depends on the receptor involved, the fitness cost of resistance, and whether resistance changes antibiotic susceptibility or virulence [8,25]. Serial isolate collection is therefore essential to determine whether resistance represents loss of therapeutic activity, an exploitable evolutionary shift, or both.

The evidence favors development through centralized or networked phage libraries rather than ad hoc product acquisition. A clinically useful library should include whole-genome sequencing, exclusion of lysogeny and undesirable genes, host-range annotation, production history, titer and stability data, endotoxin and sterility results, PAS profiles, and prior clinical-use information [24,27]. For acute intensive-care indications, turnaround time from isolate

receipt to qualified product delivery may be as important as nominal in vitro activity.

Future evaluation should not be restricted to conventional fixed-product parallel-group trials. Adaptive platform trials, registry-embedded randomized components, N-of-1 sequences in stable chronic disease, and prospective registries with target-trial emulation may preserve isolate matching while improving comparability. Common laboratory rules, product-quality standards, predefined outcome definitions, independent endpoint assessment, and transparent reporting of unsuccessful cases are necessary regardless of design.

6. Proposed Minimum Clinical-Laboratory Framework

The following framework is a review-derived proposal rather than an established universal clinical standard:

- A fresh clinical isolate with strain-level identification, antimicrobial susceptibility testing, and confirmation that the recovered organism is clinically relevant.
- Phage susceptibility testing using complementary methods, preferably a plaque-based assay or efficiency of plating together with liquid growth kinetics; a spot test alone should not determine eligibility.
- Prospective assessment of phage-antibiotic interactions when phages are used with a defined antibiotic regimen, with explicit reporting of concentrations, sequence, timing, and interpretation criteria.
- Whole-genome characterization of therapeutic phages, including exclusion of lysogeny, toxin, antimicrobial-resistance, and other undesirable genes.
- Route-specific quality control, including identity, titer, sterility or bioburden, endotoxin, stability, storage conditions, and manufacturing traceability.
- A predefined treatment plan describing route, dose, frequency, duration, concomitant antibiotics, source control, and criteria for modification or discontinuation.
- Baseline and longitudinal cultures with repeat susceptibility testing when the target organism persists or recurs.
- Assessment of neutralizing antiphage activity when technically feasible in chronic infection, repeated exposure, or systemic administration.
- Prospectively defined clinical, microbiological, functional, and safety endpoints with a fixed follow-up schedule.

For cystic fibrosis airway infection, preferred endpoints include sputum bacterial burden, ppFEV1, pulmonary exacerbations, systemic antibiotic exposure, respiratory symptoms, hospitalization, and microbiome disruption. For bloodstream or intensive-care infection, relevant endpoints include time to clearance of bacteremia, 14- or 28-day mortality, organ dysfunction, vasopressor-free or ventilator-free days, adequacy of source control, and serious adverse events.

7. Limitations

The evidence base is dominated by compassionate-use cohorts and case reports, with strong risks of selection, confounding, outcome-assessment bias, and selective publication. Successful or unusual cases are more likely to be reported than routine failures.

Intervention heterogeneity was substantial. Studies differed in pathogen, infection site, phage source, matching procedure, formulation, titer, route, antibiotic co-therapy, source control, treatment duration, and outcome definition. Pooling would therefore produce a summary estimate with limited biological meaning.

The protocol was not prospectively registered. Eligibility criteria and synthesis rules were standardized for this revision, but the absence of prospective registration limits confidence regarding the chronology of decisions.

Publication and participant overlap was assessed at the report level. Three linked case reports were nested within larger series and were not counted independently. One possible partial overlap between two expanded-access series could not be confirmed because explicit patient-level linkage was unavailable; numerical outcomes were therefore not summed across those reports.

Outcome definitions and adverse-event ascertainment were inconsistent. Long-term safety, immune neutralization, microbiome effects, and durability of microbiological response remain incompletely characterized.

8. Conclusion

Personalized phage therapy for drug-resistant and otherwise difficult-to-treat bacterial infections has progressed beyond isolated biological speculation. Human studies demonstrate operational feasibility, generally acceptable short-term tolerability, and repeated clinical and microbiological signals, particularly when phages are matched to the patient isolate and integrated with antibiotics and source control. Nevertheless, certainty of evidence for effectiveness remains very low because direct evidence is dominated by uncontrolled compassionate-use experience, heterogeneous co-interventions, potential report overlap, and selective publication.

The most scientifically defensible development model is adjunctive precision infectious-disease care rather than replacement of antibiotics. This model requires a matched and quality-controlled phage preparation, optimized antibacterial therapy, appropriate source control, dynamic microbiological monitoring, planned assessment of resistance and heteroresistance, and attention to antiphage immunity. Evidence-based implementation will depend on standardized susceptibility procedures, transparent reporting of both successes and failures, route-specific manufacturing standards, centralized phage libraries, and adaptive or registry-embedded trials that preserve individual matching while improving causal inference.

9. Declarations

Protocol registration. The protocol was not prospectively registered; this is acknowledged as a methodological limitation.

Funding. No specific funding was declared for preparation of this review.

Conflicts of interest. The authors declare no conflicts of interest.

Data availability. All outcome data synthesized in this review are derived from the cited publications. Search strategies, study-selection counts, full-text exclusion reasons, and the report-overlap matrix are presented in the manuscript. Screening and extraction materials are

available from the corresponding author on reasonable request.

Author contributions. A detailed CRediT statement was not provided in the source manuscript.

Ethics. Ethics approval was not required because the review used data from published studies and did not involve new participant-level data collection.

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Appendix 1. Database-Specific Search Strategies

The following strategies define the reproducible search framework used for this revision. Exact platform versions, execution dates, and source-specific yields should be checked against the archived search exports before submission.

Source	Full strategy or reproducible procedure
PubMed/MEDLINE	("Bacteriophage Therapy"[MeSH] OR "phage therapy"[tiab] OR bacteriophage*[tiab] OR phagotherapy[tiab] OR "therapeutic phage"[tiab] OR "therapeutic phages"[tiab]) AND (personalized[tiab] OR personalised[tiab] OR individualized[tiab] OR individualised[tiab] OR tailored[tiab] OR customized[tiab] OR customised[tiab] OR "compassionate use"[tiab] OR "expanded access"[tiab] OR susceptibility[tiab] OR "host range"[tiab] OR "phage-antibiotic"[tiab]) AND (infection*[tiab] OR bacteremia[tiab] OR sepsis[tiab] OR MDR[tiab] OR XDR[tiab] OR PDR[tiab] OR "multidrug-resistant"[tiab] OR "drug-resistant"[tiab] OR "difficult-to-treat"[tiab])
Embase (Elsevier)	('phage therapy'/exp OR 'bacteriophage'/exp OR 'phage therapy':ti,ab OR bacteriophage*:ti,ab OR phagotherapy:ti,ab) AND (personalized:ti,ab OR personalised:ti,ab OR individualized:ti,ab OR tailored:ti,ab OR customized:ti,ab OR 'compassionate use':ti,ab OR 'expanded access':ti,ab OR susceptibility:ti,ab OR 'host range':ti,ab OR 'phage antibiotic':ti,ab) AND (infection*:ti,ab OR sepsis:ti,ab OR bacteremia:ti,ab OR MDR:ti,ab OR XDR:ti,ab OR PDR:ti,ab OR 'multidrug resistant':ti,ab OR 'drug resistant':ti,ab OR 'difficult to treat':ti,ab)
Scopus	TITLE-ABS-KEY(("phage therapy" OR bacteriophage* OR phagotherapy OR "therapeutic phage*") AND (personalized OR personalised OR individualized OR individualised OR tailored OR customized OR customised OR "compassionate use" OR "expanded access" OR susceptibility OR "host range" OR "phage-antibiotic") AND (infection* OR sepsis OR bacteremia OR MDR OR XDR OR PDR OR "multidrug-resistant" OR "drug-resistant" OR "difficult-to-treat"))
Web of Science Core Collection	TS=(("phage therapy" OR bacteriophage* OR phagotherapy OR "therapeutic phage*") AND (personalized OR personalised OR individualized OR individualised OR tailored OR customized OR customised OR "compassionate use" OR "expanded access" OR susceptibility OR "host range" OR "phage-antibiotic") AND (infection* OR sepsis OR bacteremia OR MDR OR XDR OR PDR OR "multidrug-resistant" OR "drug-resistant" OR "difficult-to-treat"))
Cochrane CENTRAL	("phage therapy" OR bacteriophage* OR phagotherapy):ti,ab,kw AND (personalized OR personalised OR individualized OR tailored OR customized OR "compassionate use" OR susceptibility OR "host range"):ti,ab,kw AND (infection* OR MDR OR XDR OR PDR OR "drug resistant" OR "difficult to treat"):ti,ab,kw
ClinicalTrials.gov	Condition/disease: bacterial infection OR antimicrobial-resistant infection. Other terms: (phage therapy OR bacteriophage) AND (personalized OR susceptibility OR MDR OR XDR OR PDR). Study type: interventional and observational. Recruitment status: all. Export all records and document search date.
Citation searching	Screen reference lists of all included reports and relevant systematic reviews. Perform forward citation searching for the principal personalized cohorts and randomized trials. Record platform, date, seed article, and number of unique reports identified.

The search-strategy table combines controlled vocabulary and free-text terms for phage therapy, personalization, susceptibility, expanded access, and drug-resistant infection. Separate syntax is provided for each bibliographic platform, while trial-register and citation-search procedures are specified as reproducible workflows. Source-specific exports and search dates should remain archived with the screening record to permit independent verification and future updating.

Appendix 2. Recommended Supplementary Package for Submission

- Supplementary File S1: completed PRISMA 2020 checklist with page references.
- Supplementary File S2: full database strategies, search dates, platforms, and record counts by source.
- Supplementary Table S1: report-level full-text exclusions with one primary reason per report, reconciled against the original screening log.
- Supplementary Table S2: complete study-level extraction table.
- Supplementary Table S3: outcome-level RoB 2 assessments for randomized trials.
- Supplementary Table S4: JBI domain assessments for cohorts, case series, and case reports.
- Supplementary Table S5: expanded report-to-study overlap matrix with patient-level linkage evidence where available.
- Supplementary File S3: deduplication and screening audit trail or repository link.