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# Bacteriophage: A Promising Alternative Against AMR

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## Introduction:

Antimicrobial resistance (AMR) has emerged as one of the gravest threats to modern medicine, undermining decades of progress in infectious disease control. It is cited by the World Health Organization (WHO) as one of the top 10 threats to global health. In 2019 alone, AMR was associated with approximately 4.95 million deaths, including 1.27 million directly attributable to resistant bacterial infections. This makes AMR a leading cause of death worldwide, surpassing HIV/AIDS (0.86 million deaths) and malaria (0.64 million deaths) in the same year. Projections suggest that if the trend continues unchecked, AMR could cause 10 million deaths annually by 2050, representing a profound human-cost escalation.

## Livestock and Animal Burden:

While the quantitative burden of AMR in animals is not yet globally mapped, its effects in livestock are already both profound and alarming. Over 70% of all antimicrobials globally are used in farm animals frequently for growth promotion and disease prevention – not just treatment. This widespread use contributes to emerging resistance in key pathogens – *Salmonella*, *E. coli*, *Campylobacter in poultry*, and severe swine dysentery in pigs. In some outbreaks, swine dysentery, resistant to conventional treatment, has caused up to 90% morbidity and 30% mortality in weaned pigs.

## Animal to Human Transmission and the One Health Paradigm:

Antimicrobial resistance in livestock doesn't stay on the farm; it seeps into the environment and crosses over to humans via food chains, direct contact, and environmental pathways. For example, substandard veterinary medicine and antibiotic misuse have been traced in zoonotic infections and veterinary in for Animal Health (OIE) acknowledges that while human-related AMR mortality is well-documented, the animal health burden is not yet quantified globally – though numerous projects are underway to address this gap.

The failure of conventional antibiotics to treat resistant infections highlights the urgent need for

alternative therapeutic strategies. Among the most promising options is bacteriophage therapy – the use of viruses that are specifically larger and kill bacteria.

## What are Bacteriophages?

Bacteriophages, often referred to simply as phages are viruses that infect and replicate within bacteria. They are considered the most abundant biological entities on Earth, with an estimated amount of $10^{31}$ phage particles present in the biosphere, outnumbering bacteria by approximately tenfold. Phages are naturally found in diverse ecosystems, including soil, ocean, sewage, and even within the microbiomes of humans and animals.

Phages display a wide variety of shapes and structures, which generally include a nucleic acid core (DNA or RNA) enclosed in a protein capsid and, in many cases, a tail structure that facilitates infection of bacterial cells.

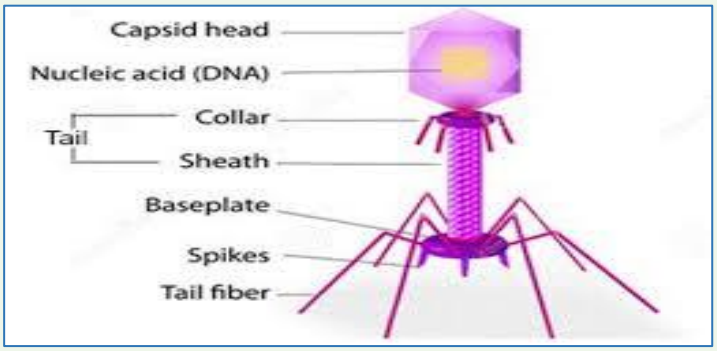


Fig 1 : Basic outline of Bacteriophage structure with its morphological features
(Source : https://thumbs.dreamstime.com/z/virus-bacteriophage-model-isolated-vector-illustration-description-56397925.jpg)

## Classification of Bacteriophage:

Bacteriophages are classified mainly based on their morphology, genetic material, and replication strategies. The official classification is maintained by the International Committee on Taxonomy of Viruses (ICTV). Below is a structured overview of phage classification.

| Basis of classification | Category | Characteristics | Examples |
|---|---|---|---|
| **Genetic material** | dsDNA | Most common type of phages | T4, 2 phage |
| | ssDNA | Small genome | X174 |
| | ssRNA | Icosahedral, RNA genome | MS2. Qβ |
| | dsRNA | Rare, enveloped | 6 |
| **Morphology (ICTV/ Traditional)** | **Tailed phages-** (Caudoviricetes): 96% of known phages | | |
| | Myoviridae | Contractile tail, large head | T4 phage |
| | Siphoviride | Long, flexible, non-contractile tail | $^{x}$phage |
| | Podoviridae | Short, Stubby tail | T7 phage |
| | **Non-tailed phages** | | |
| | Inoviridae | Filamentous, flexible | M13 |
| | Microviridae | Small, icosahedral, ssDNA | |
| | Cystoviridae | Enveloped, dsRNa | 6 |
| | Leviviridae | Icosahedral, ssRNA | MS2 |
| | Tectiviridae | Icosahedral with lipid membrane | PRDI |
| | Plasmaviridae | Pleomorphic, lipid-containing | MV-12 |
| **Life cycle** | Lytic (Virulent) | Multiply rapidly, lyse host cell | T4 phage |
| | Lysogenic (Temperate) | Integrates as a prophage, may enter the lytic cycle later | $^{x}$phage |

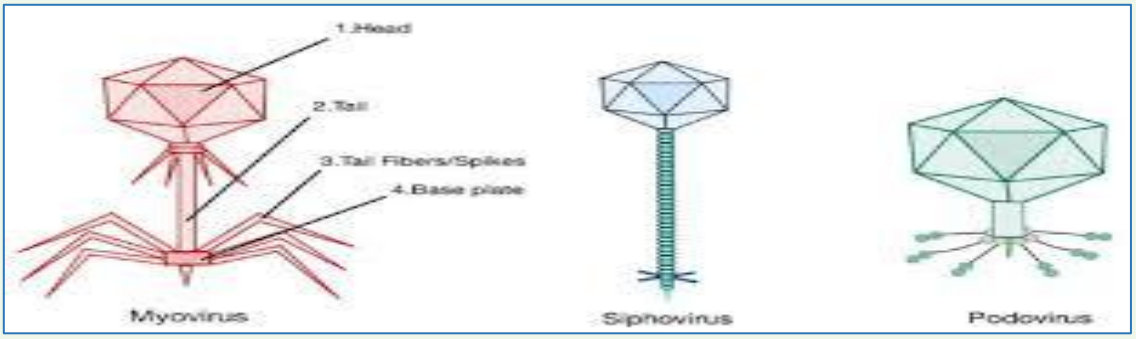


Fig.2 : Tailed Bacteriophages of Caudoviricetes

(Source : https://www.researchgate.net/publication/354292829/figure/fig1/AS:1143128117108815 8@1688029734485/Tailed-bacteriophages-The-Caudovirales-order-consist-of-three-families-a-Myoviridae.tif)

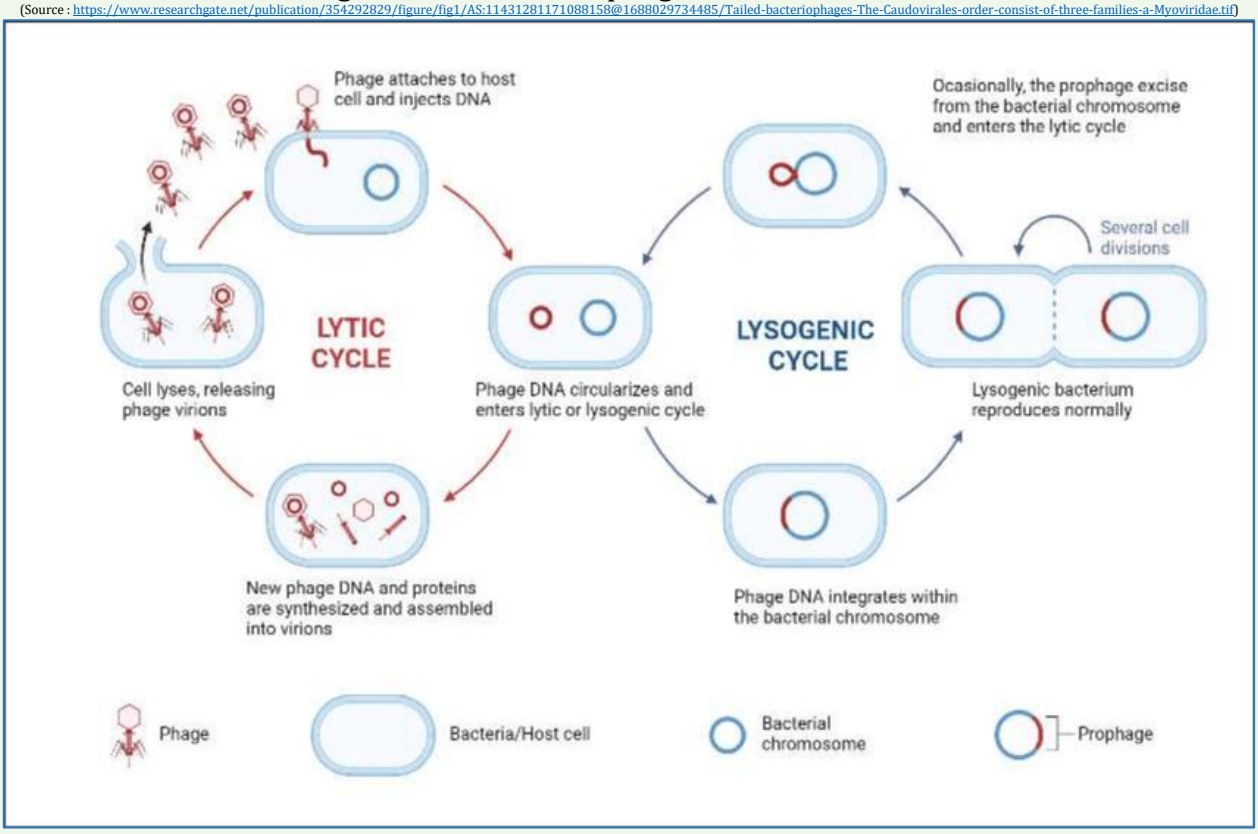


Fig. 3 : Lytic and lysogenic reproduction cycles of certain bacteriophages

(Source : https://www.bartleby.com/questions-and -answers//lytic-cycle-lysogenic-cycle-phage-dna-bacteriophage-bacterial-chromosome-new-phages-phage-injects-it/0e7cffec-9809-4a62-b332-82ed60a08879)

**Phages interact with bacteria through two major life cycles:**

- **Lytic Cycle:** The phage attaches to the bacterial cell receptors, injects its nucleic acid, hijacks the host machinery, and produces new virions. This culminates in host cell lysis, releasing dozens to hundreds of new phages. Classic examples include T4 phage infecting E. coli.
- **Lysogenic Cycle :** Some phages, termed as temperate phages, integrate their DNA into the bacterial genome as a prophage. This latent state can persist until triggered by stress (e.g., UV radiation, antibiotics), at which point the phage shifts to a lytic cycle. The phage is the prototypical model for lysogeny.

For therapeutic purposes, strictly lytic phages are preferred, as lysogenic phages risk transferring virulence or antibiotic resistance genes through transduction.

## Mechanisms of Bacterial Killing:

**Phage infection involves highly specific stages:**

1. **Adsorption –** Tail fibres recognise and bind to receptors such as lipopolysaccharides, teichoic acids, or membrane proteins. Example: *Pseudomonas aeruginosa* phages often target Type IV pili or lipopolysaccharides.
2. **Penetration and Genome Injection** – The phage injects its DNA /RNA into the host.
3. **Replication and Assembly** – The host's transcription/translation machinery is redirected to produce viral proteins and genomes.
4. **Host Cell Lysis** – Phage-encoded enzymes like endolysins and holins degrade the bacterial cell wall, leading to the release of progeny phages.

Notably, endolysins themselves have been developed as promising antimicrobials; for example, the endolysin CF-301 (exobases) demonstrated potent activity against Methicillin-resistant *Staphylococcus aureus* (MRSA) in clinical trials.

## Why bacteriophage therapy matters?

This dual AMR crisis – threatening both humans and animals – underscores the urgent need for alternatives to conventional antibiotics. Bacteriophage therapy emerges as a tailored, adaptive and potentially scalable solution. By acknowledging the intricate One Health interplay – humans, animals and the environment phage therapy not only address isolated infections but also holds transformative potential in mitigating AMR across interconnected domains. Phages offer:

- **Target specificity and reduced dysbiosis –** Phages recognise strain or species-specific receptors (LPS, capsule polysaccharides, pili, outer membrane proteins), allowing targeted elimination of pathogen. This reduces the risks of antibiotic-associated dysbiosis, opportunistic infections (e.g. *Clostridioides difficile*) and downstream selection for resistance in bystander organisms.
- **Self-amplification and auto-dosing –** Unlike conventional drugs, where therapeutic concentration declines with clearance, phages replicate at the infection site proportional to available susceptible bacteria. This "autodosing" can produce high local multiplicities of infection (MOI) and prolong effective exposure without escalating systemic dosing, particularly useful for poorly vascularized lesions.
- **Adaptive capacity and evolvability –** (A dynamic countermeasure to bacterial evolution of resistance) – In contrast to small antibiotic molecules, when bacteria mutate its receptors or use CRISPR/Cas or restriction-modification systems, phages evolve altered adsorption proteins or anti-CRISPR proteins, thereby capacitating the real-time evolutionary adaptation.
- **Unique antibiofilm activity –** Phages can penetrate and disrupt the bacterial biofilms via multiple mechanisms: enzymatic degradation of extracellular polymeric substances (EPS) by phage-encoded depolymerases, localised lytic amplification within biofilm microcolonies, and induction of biofilm-dispersal phenotypes. These properties address a key limitation of antibiotics, which often fail to

eradicate biofilm-embedded bacteria.

- **Modular mechanisms (lytic enzymes and payloads) –** Phage components (endolysins) are themselves drug candidates: endolysins degrade peptidoglycan and rapidly kill Gram-positive pathogens when applied exogenously. Engineered phages can deliver payloads (CRISPR nucleases, toxin inhibitors) to selectively remove resistance genes or essential virulence loci.

## Phage based therapies for AMR infections:

**1. Classical Phage Therapy (Natural Lytic Phages):**

- **Concept:** Using naturally occurring strictly lytic phages against resistant pathogens.
- **Advantages:** High specificity, self-amplification at infection sites, ability to lyse even MDR bacteria.
- **Examples:**
  - → ***Acinetobacter baumannii :*** Compassionate-use phage cocktails successfully treated MDR infections in ICU patients.
  - → ***Pseudomonas aeruginosa :*** Inhaled phage therapy showed safety and reduction in bacterial load in cystic fibrosis patients.
  - → ***Mycobacterium abscessus :*** Engineered lytic phages rescued a cystic fibrosis patient with a disseminated infection resistant to all antibiotics.

**2. Phage – Antibiotic Synergy (PAS):**

- **Concept:** Phages used in combination with antibiotics show synergistic effects.
- **Mechanisms:** Antibiotics stress bacteria, making them more susceptible to phage adsorption. Phage infection disrupts bacterial resistance mechanisms, lowering MICs for certain antibiotics.
- **Evidence:** *In vitro* and animal studies show phage-antibiotic synergy against MDR *E. coli*, *Klebsiella pneumonia*, and *A. baumannii*

**3. Phage-Derived Enzymes (Endolysins & Depolymerases):**

- **Endolysins:** Hydrolytic enzymes produced by phages to break the bacterial cell walls. Exebacase (CF-301), though, has potent anti Staphylococcal and anti-biofilm activity, but when tested in. MRSA bacteremia/endocarditis, its phase 3 trial gave mixed results.
- **Depolymerases:** Enzymes that degrade the bacterial capsules or biofilms thereby broadening the antibiotic access to bacteria. Studies reported that K-type specific depolymerases targeting carbapenem-resistant *Klebsiella pneumoniae* improved antibiotic efficacy in preclinical models.

**4. Engineered & Synthetic Phages:**

- **CRISPR – enhanced phages:** These are modified to carry CRISPR systems that cut essential bacterial genes. Example. LBP-EC01 (Loss Biosciences) – a CRISPR–Cas3–enhanced phage cocktail against E coli in urinary tract infections dosing with TMP-SMX, progressing through phase 2 trials, produced rapid, durable *E. coli* reductions and symptom resolution, with consistent pharmacokinetics in urine/blood.

- **Synthetic Phages:** Genetically optimized for broader host range, increased stability, or reduced immune clearance.
- **Advantages:** Overcome natural host-range limits, reduce resistance emergence.

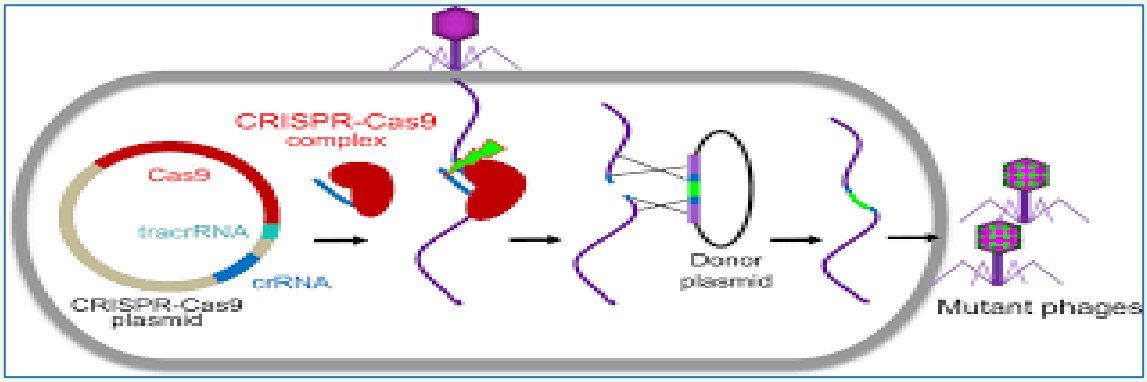


**Fig.** 4 : Outline for production of CRISPR-Cas engineered phages
**(Source:** https://www.researchgate. Net/profile/Himanshu-Batra 2/ publication /332848432/figure/fig2/AS:754519734493186@1556902931643/CRISPR-Cas-based-phage-engineering-The-formed-CRISPR-Cas9-complex-specifically-binds.png)

## 5. Formulation & Delivery Innovation:

- **Encapsulation in hydrogels, liposomes or nanoparticles** improves phage stability and controlled release. Oral microencapsulation protects phages from gastric acid , enabling gut microbiome -targeted applications. Examples include room temperature stable hydrogel microbeads. GI-stable Salmonella phage microspheres and chitosan-encapsulated MRSA phages for poultry.
- **Nebulised phage therapy**: for respiratory infections (e.g., cystic fibrosis caused by *P.aeruginosa*)

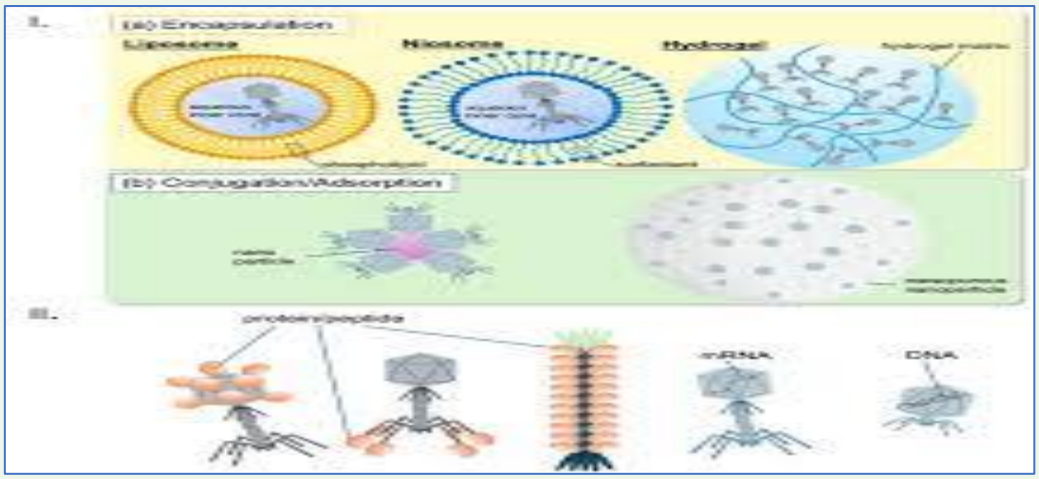


**Fig.5:** An outline of Phage therapy and Phage based drug development
(Sources: http:// www.mdpi.com /antibiotics-13-00870/article_deploy/html/images/antibiotics-13-00870-g002.png)

## 6. Personalized Phage Banks & Rapid Matching:

- **Phage Bank Model (Adaptive Phage Therapeutics):** Maintains 2 large GMP phage library; clinicians select active phages against a patient's isolate via rapid susceptibility testing (phagogram)
- **Magistral Phage Framework (Belgium):** Physicians can prescribe custom patient specific phages prepared in pharmacies under quality-monitored conditions for individualized therapy.
- **Rapid Phagograms:** emerging hydrogel-based, capillary-wave micro-bioreactor, and colorimetric platforms aim to bringsame-week or even same-day tailoring of phage therapy for resistant infections.

**7. One Health Applications (Human+Veterinary+Environmental):**

- **Veterinary Use:** Phage therapy is directly applicable to livestock and aquaculture domains that account for the majority of the global antimicrobial consumption, ultimately reducing antibiotic pressure, thereby indirectly lowering human AMR selection. Examples under study which gave promising results in the recent past include phage control of bovine mastitis pathogens (*Staphylococcus aureus*, *E.coli*), reduction of *Campylobacter / Salmonella* carriage in poultry and prevention of vibriosis in shrimp farms.
- **Food Safety:** FDA-approved phage preparations (e.g.List Shield ™ for Listeria) are already applied in food processing and ready-to-eat foods to reduce food-borne pathogens, which in turn combat transmission of resistant bacteria through the food chain.
- **Environmental Applications:** As phages are ubiquitous and biodegradable, environmental phage based biocontrol may limit antibiotic residues and resistant strains in agricultural runoff as well as wastewater compared with continuous antibiotic use (e.g. Phage biocontrol in aquaculture to reduce Vibrio infections).

## Scientific Challenges and Current Research Advances:

1. **Narrow host range and diagnostic needs:** A therapeutic phage effective for one clinical isolate may be inactive against another strain of the same species. To overcome this drawback, development of phage banks, rapid phagograms (phage susceptibility testing) and engineered broad – host – range phages or cocktails to widen coverage can be undertaken.
2. **Host immune interactions and clearance:** Preexisting or induced anti-phage antibodies can neutralise phages, particularly with systemic administration. In response to this problem local/topical delivery (wounds, inhalation, bladder instillation) PE Gylation/encapsulation to shield phages, and engineering phages to reduce immunogenic surface motifs can be done to avoid host-immune response.
3. **Bacterial resistance to phages:** To mitigate bacterial mutation of receptors or inactivation of defense systems, use phage cocktails targeting multiple receptors in bacteria, alternating or sequential phage therapy, and combining phages with antibiotics counteract resistance evolution more effectively.
4. **Horizontal gene transfer risks:** In phage therapy, temperate phages can mediate transduction of virulence or resistance genes. To avoid this issue, strict selection of obligately lytic phages with genome sequencing to exclude transducing elements and lysogeny-associated genes through engineering should be carried out.
5. **Standardization, manufacturing and regulatory complexities:** Biological variability of phage preparations raises quality control and regulatory challenges. GMP phage production pipelines,

validated potency assays and novel regulatory frameworks (e.g. magistral / pharmacy-based models) to allow personalized phage medicines while ensuring safety, can handle the regulatory complexities.

6. **Phage PK/PD modeling and dose optimization:** Traditional antibiotic pharmacokinetic parameters (Area under curve (AUG)/ Minimum inhibitory concentration (MIC)] can't be applied directly to phages. Hence Optimal dosing strategies should be predicted based on development of integrated host-pathogen-phage mathematical models that incorporate bacterial growth rates, spatial heterogeneity (biofilms), immune clearance and replication dynamics.

## What can be done in future?

- **Near term:** personalised, compassionate-use and locally formulated phage therapies for refractory infections; topical and inhaled formulations for localised disease.
- **Medium term:** GMP, manufactured phage cocktails for specific syndromes (e.g. chronic pseudomonas in cystic fibrosis, prosthetic joint infections) and regulatory pathways for adjunctive enzyme/phage products.
- **Long term:** integration into One-Health AMR strategies - replacing prophylactic antibiotic use in certain agricultural settings, lowering environmental antibiotic loads, and providing modular countermeasures to emerging resistant clones through flexible phage libraries and engineered platforms.

## Conclusion:

Bacteriophage therapy is a scientifically compelling alternative to antibiotics in the fight against antimicrobial resistance (AMR). Lytic bacteriophages, especially when leveraged as phage cocktails, offer high specificity and evolutionary adaptability, enabling them to target multidrug-resistant (MDR) pathogens while largely sparing beneficial communal flora. This specificity supports "autodosing", whereby phages self-replicate at infection sites, achieving high local concentrations and improving clearance of biofilm-associated infections. Clinical applications of phage cocktails have shown promise in complex cases such as MDR *Pseudomonas aeruginosa* prosthetic joint infections and *Acinetobacter baumannii* septicemia. Furthermore, Engineered phages bearing CRISPR-Cas payloads can select and eliminate resistance genes and phage-derived enzymes like endolysins and depolymerases, effectively disrupting biofilm and cell wall integrity to restore antimicrobial sensitivity.

The relevance of phage therapy extends beyond human medicine and aligns with One Health priorities. The overwhelming use of antimicrobials in livestock – responsible for an estimated 131,109 tonnes of antimicrobial use in food animals in 2013 and projected to rise to 200,235 tonnes by 2030-drives the emergence of AMR in animal populations, with spillover effects on human health. Although precise global animal-specific mortality data remain unquantified, international bodies including the World Organization for Animal Health (WOAH) are actively collaborating with the Global Burden of Animal

Diseases initiative to assess the burden of AMR in livestock Additionally, WOAH's 2025 global report warns that AMR threatens food security for up to 2 billion people and could incur up to USD 100 trillion in economics losses by 2050.

In this context, phage cocktails – supported by rapid diagnostics (phagograms) and GMP-scale manufacturing offer a scientifically grounded, dynamic solution to reducing reliance on antibiotics across sectors, curbing AMR in humans, animals and the environment alike.

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