BG Pulse Journal USA
ISSN:1947-2536 http://www.bgpulseusa.com/index.php/bg
BG PULSE JOURNAL

ANTIBIOTIC RESISTANCE: A GLOBAL PROBLEM AND BACTERIOPHAGE THERAPY AS AN ALTERNATIVE SOLUTION

Shakirbek Yusupovich Zakirov
PhD (Candidate of Medical Sciences),
Associate Professor, Department of Microbiology,
Virology and Immunology,
Urgench State Medical Institute, Uzbekistan
Diana Jamoladdinovna Ozodova
2nd-year student, Faculty of Medicine, Urgench State Medical Institute, Uzbekistan
Corresponding author: **Zakirov Sh.Y.**, doc_zakiroff@mail.ru
co-author: ozodovadiana10@gmail.com;
tel.: +998 91 437 54 84
doi:https://doi.org/10.5281/zenodo.24170897

Abstract. Antimicrobial resistance (AMR) is the ability of bacteria to withstand the action of antibiotics, and the World Health Organization regards it as one of the most serious threats to global health. According to the Global Research on Antimicrobial Resistance (GRAM) study, AMR was directly responsible for 1.14 million deaths and associated with 4.71 million deaths in 2021; annual attributable deaths are forecast to reach 1.91 million by 2050. Resistance arises through enzymatic inactivation, target modification, efflux pumps, reduced membrane permeability, biofilm formation and horizontal gene transfer, and is accelerated by inappropriate and excessive antibiotic use. Drawing on the GRAM project and the WHO GLASS 2025 report, this narrative review examines the global burden of AMR, the factors driving its spread and the WHO priority pathogens. Bacteriophage therapy is analysed separately: its mechanism of action, advantages (high specificity, activity against multidrug-resistant strains and biofilms, synergy with antibiotics), clinical experience and unresolved challenges (narrow host range, phage resistance, limited randomised evidence). We conclude that phage therapy is a promising direction for infections caused by multidrug-resistant bacteria, but robust clinical evidence is still limited; it should be regarded as a complement to antibiotics within a comprehensive strategy.

Keywords: antimicrobial resistance; AMR; bacteriophages; phage therapy; biofilm; multidrug-resistant bacteria; One Health.

1. Introduction

The discovery of antibiotics was among the greatest achievements of twentieth-century medicine. Beyond treating infections, antibiotics underpin the safety of surgery, chemotherapy, organ transplantation and the care of premature infants. However, the evolution of bacterial resistance is a natural process, and the excessive and inappropriate use of antibiotics in humans, livestock and agriculture has sharply accelerated it [1,2]. As a result, infections that were once easily treated are becoming difficult to cure, and experts warn of a “post-antibiotic era” in which common infections and routine operations could again become dangerous.

In this setting, alternatives and complements to antibiotics are being sought. Among them, bacteriophages – viruses that selectively infect and kill bacteria – occupy a special place [7].

Aim. To present the scale of the AMR problem on the basis of current international data and to critically assess the possibilities and limitations of phage therapy.

2. Materials and Methods

This article is a narrative literature review. Data were drawn from three groups of sources: (1) WHO and United Nations documents (the GLASS 2025 report, the 2024 priority pathogens list and the 2024 UN political declaration on AMR); (2) GRAM publications in The Lancet; and (3) clinical studies, systematic reviews and trial-registry data on bacteriophage therapy in international journals. Priority was given to official reports and peer-reviewed publications from 2019–2026. Statistical values are reproduced as given in the original sources.

3. Global Burden of AMR

The largest analysis of AMR has been produced by the GRAM project. Its 2019 assessment showed that deaths directly attributable to AMR (about 1.27 million) exceeded those from HIV/AIDS or malaria [1]. The 1990–2021 analysis and forecast to 2050, published in The Lancet in 2024, found that AMR has caused at least one million deaths every year since 1990; in 2021, 1.14 million deaths were directly attributable to AMR and 4.71 million were associated with it [2]. Deaths from carbapenem-resistant gram-negative bacteria rose from 127,000 in 1990 to 216,000 in 2021 [2].

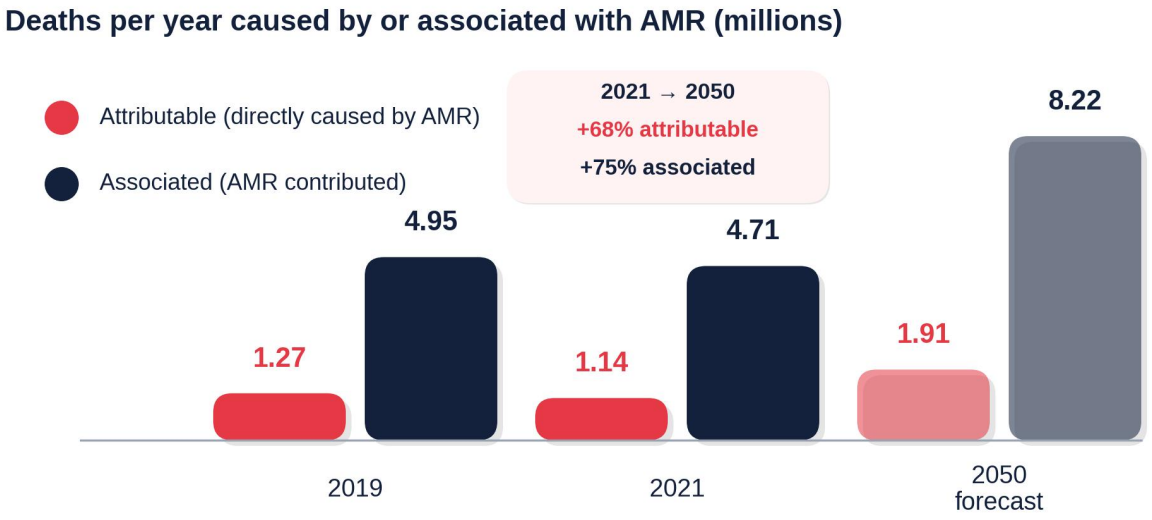


Figure 1. Annual deaths attributable to and associated with AMR in 2019 and 2021, and the forecast for 2050 (millions) [1,2].

If current trends continue, AMR is projected to directly cause more than 39 million deaths and be associated with 169 million deaths between 2025 and 2050, with annual attributable deaths reaching 1.91 million by 2050. The heaviest burden falls on South Asia (11.8 million deaths in 2025–2050) and sub-Saharan Africa. At the same time, better treatment of infections and improved access to antibiotics could avert 92 million deaths, which shows that the problem is not insoluble [2].

The WHO GLASS 2025 report is based on more than 23 million laboratory-confirmed cases from 104 countries. According to it, one in six bacterial infections worldwide and one in three urinary tract infections are caused by antibiotic-resistant bacteria (Figure 2). Resistance increased in roughly 40% of the pathogen–antibiotic combinations monitored in 2018–2023 (5–15% relative increase per year). The most dangerous trend is rising resistance to carbapenems and fluoroquinolones in gram-negative bacteria (E. coli, K. pneumoniae). The report also shows a

disproportionately high burden in low- and middle-income countries and insufficient surveillance in some regions [3].

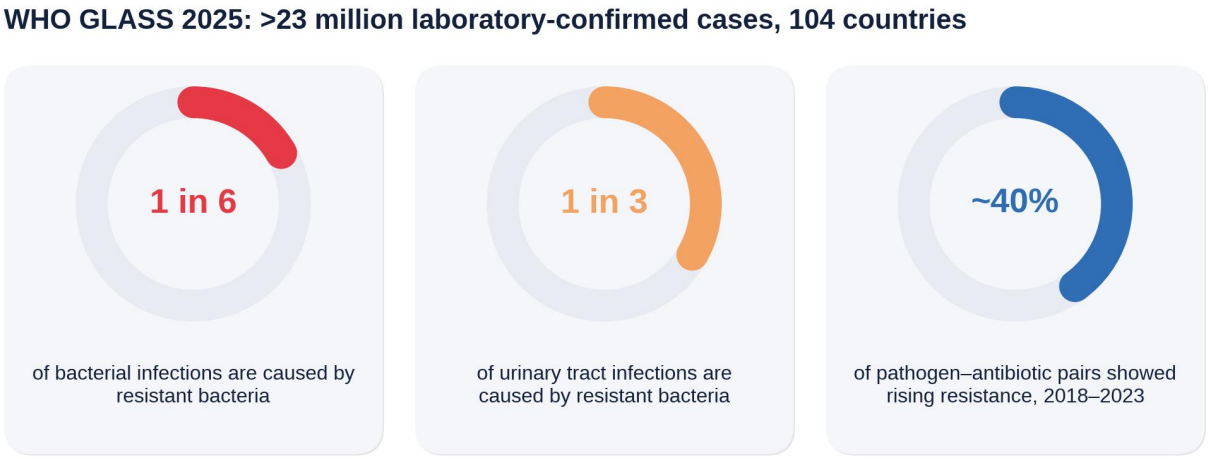


Figure 2. Key indicators of the WHO GLASS 2025 report [3].

4. Mechanisms, Drivers and Global Targets

Bacteria resist antibiotics through six principal routes (Figure 3): enzymatic inactivation of the drug, modification of its target, efflux pumps, reduced membrane permeability, biofilm formation and horizontal gene transfer, which spreads resistance genes between bacteria and species [6]. Biofilms are particularly problematic because they shelter dormant cells inside a protective matrix and are a common cause of persistent infections [5].

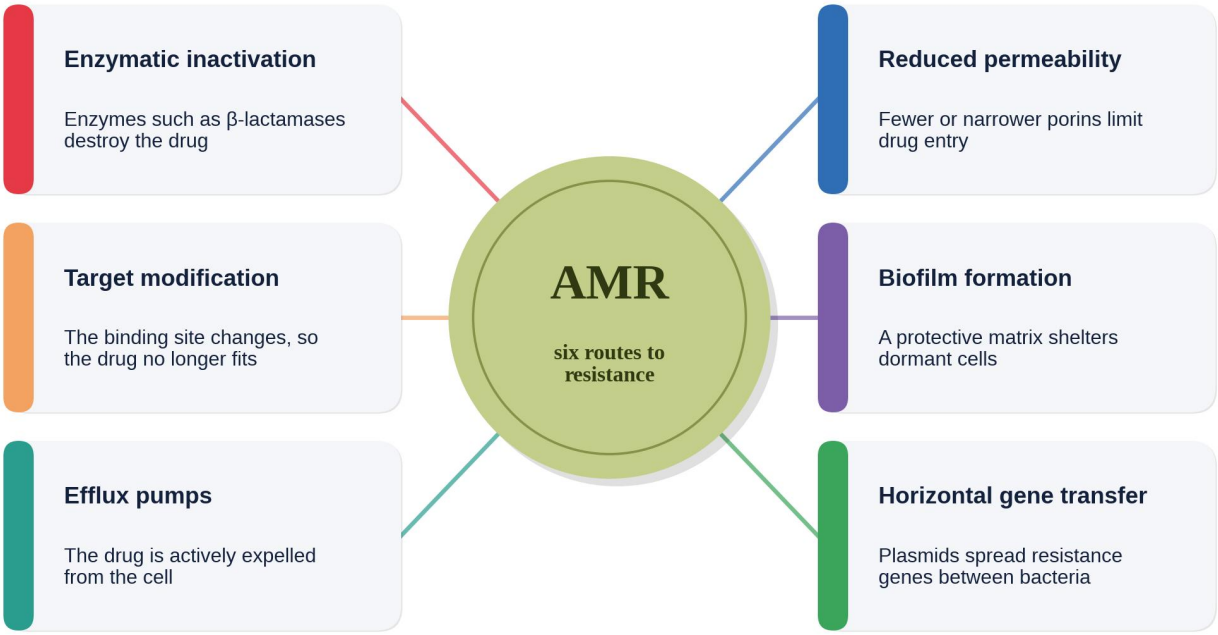


Figure 3. Mechanisms of antibiotic resistance [5,6].

AMR is a natural phenomenon, but its pace is set by human activity. The most important drivers are:

- antibiotic use without a prescription or for viral infections (colds, influenza), and failure to complete the course;
- over-the-counter sales in some countries, and substandard or falsified medicines;
- excessive use of antibiotics in livestock farming and fish farming, which is why a "One Health" approach is needed;
- weak hospital infection control and inadequate hand hygiene and sanitation;
- shortage of rapid microbiological diagnostics, leading to "blind" prescribing of broad-spectrum drugs;
- few new antibiotics, because their development is economically unattractive.

In September 2024 the UN General Assembly adopted a political declaration on AMR based on the One Health approach (human, animal and environmental health). It sets targets for 2030: a 10% reduction in AMR-related deaths from the 2019 baseline of 4.95 million; at least 70% of antibiotics used in human health drawn from the WHO Access group; funded national AMR action plans in at least 60% of countries; and water, sanitation and hygiene services in all health-care facilities [12].

5. WHO Priority Pathogens

In the WHO 2024 list of priority bacterial pathogens, the critical group includes carbapenem-resistant Acinetobacter baumannii, third-generation cephalosporin- or carbapenem-resistant Enterobacterales (E. coli, Klebsiella pneumoniae) and rifampicin-resistant Mycobacterium tuberculosis [4]. MRSA, multidrug-resistant Pseudomonas aeruginosa and resistant Neisseria gonorrhoeae also pose serious clinical problems. It is against these pathogens that new approaches, including phage therapy, are being tested most intensively.

6. Bacteriophage Therapy

Bacteriophages attach to specific receptors on a bacterial cell, inject their genome and, in the lytic cycle, multiply inside the cell and destroy it. Because their target differs from that of antibiotics, they remain active against strains resistant to conventional drugs. The steps of the lytic cycle are shown in Figure 4, and the principal strengths and challenges of the approach in Figure 5.

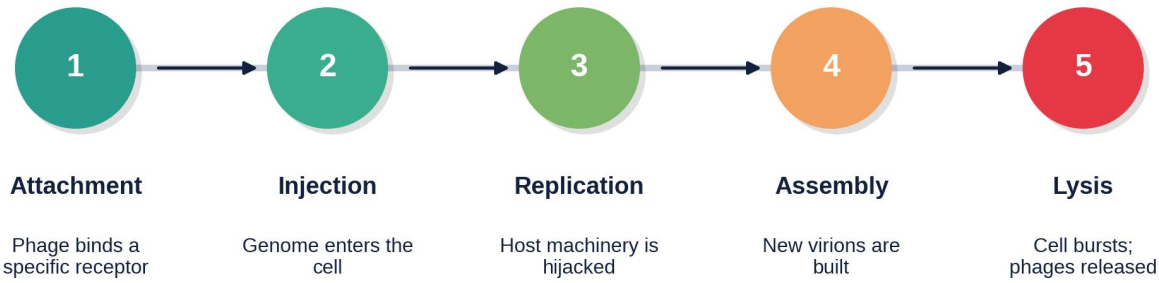


Figure 4. The lytic cycle of a bacteriophage [7].



Figure 5. Strengths and challenges of bacteriophage therapy [5,7–10,13].

Several points deserve emphasis. Some phages degrade the biofilm matrix through depolymerase enzymes [5,7], and in some cases phages can make bacteria susceptible to antibiotics again – for example, a phage targeting an efflux pump in P. aeruginosa [8]. Observational data indicate a generally good safety profile, with few severe adverse events [10]. On the other hand, bacteria defend themselves against phages through receptor mutations and CRISPR-Cas and restriction–modification systems; phage cocktails and careful phage selection may reduce this risk [7]. Regulatory frameworks designed for conventional drugs do not fit personalised therapy, and some countries (for example, Belgium) are introducing separate mechanisms.

Clinical experience. The largest dataset to date is the BT100 study, a retrospective analysis of 100 consecutive cases of personalised phage therapy for difficult-to-treat infections across several countries. Clinical improvement and eradication of the target bacteria were reported for 77.2% and 61.3% of infections, respectively (Figure 6) [13]. Eradication was about 70% less likely when no concomitant antibiotics were used, phage–antibiotic synergy was documented in vitro in 9 of 10 evaluated patients, and in vivo selection of phage resistance occurred in 7 of 16 patients, with immune neutralisation of phages in 5 of 13 screened patients [13]. These findings support combining phages with antibiotics, but the data are uncontrolled.

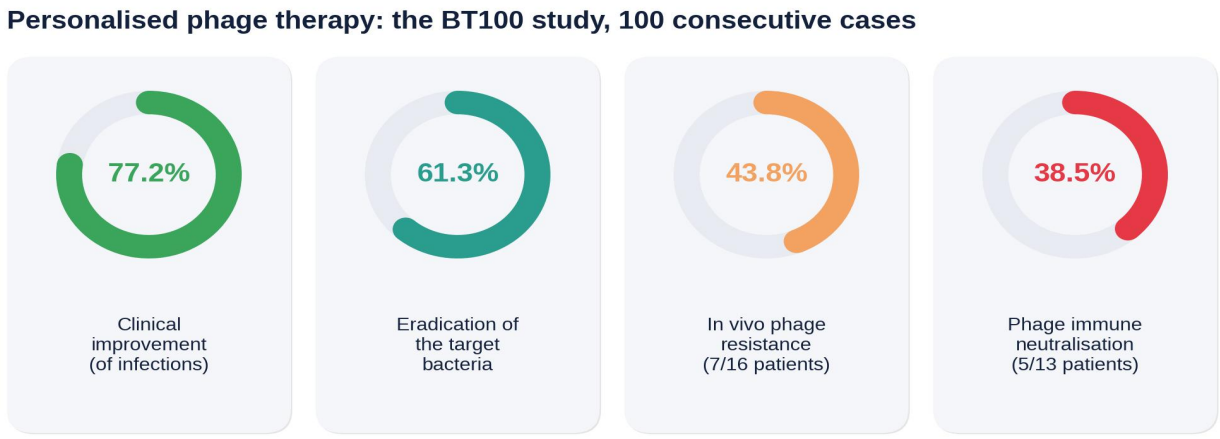


Figure 6. Outcomes of 100 consecutive personalised phage therapy cases (BT100 study) [13].

Compared with antibiotics, phages are far narrower in spectrum, have more complex pharmacokinetics and are often personalised, whereas antibiotics are ready-made products backed by large randomised controlled trials (RCTs). Most phage evidence consists of case reports, case series and small studies, and the results of RCTs such as PhagoBurn show that the technology still needs refinement [9,13].

7. Rational Antibiotic Use: the AWaRe Classification

The WHO AWaRe classification divides antibiotics into three groups (Figure 7): Access (first choice, relatively narrow spectrum, low resistance risk), Watch (higher resistance risk; only for clear indications) and Reserve (last resort for multidrug-resistant infections) [14]. The 2024 UN declaration aims to raise the share of Access antibiotics to at least 70% [12].

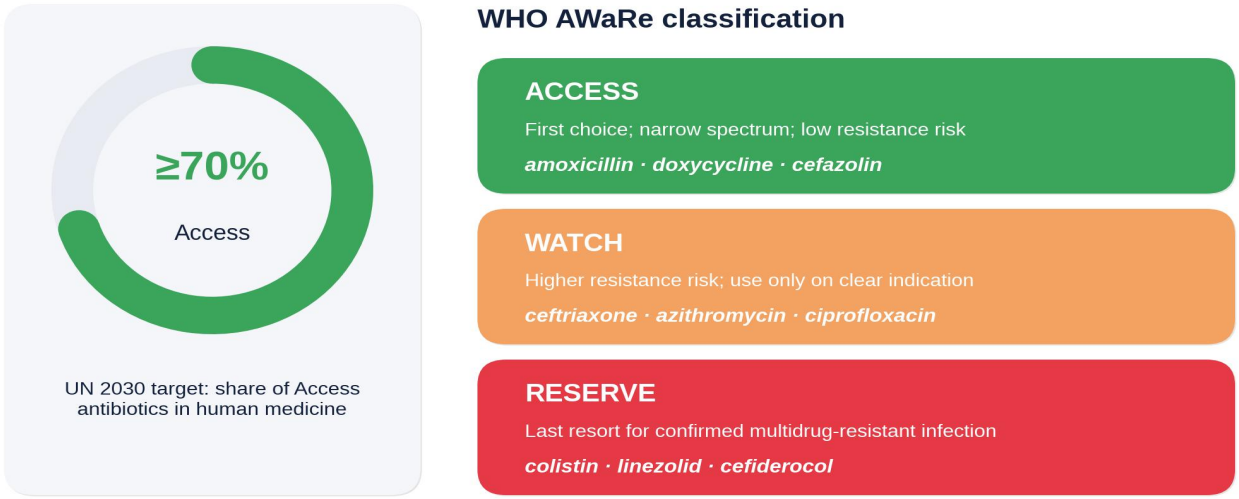


Figure 7. The WHO AWaRe classification and the UN 2030 target for Access antibiotics [12,14].

Practical rules for physicians and medical students:

• do not prescribe antibiotics for viral infections (acute respiratory viral infection, influenza, most cases of acute bronchitis);

• whenever possible, take samples (culture, susceptibility testing) before starting treatment and reassess at 48–72 hours: can therapy be stopped or narrowed?

• limit duration to the shortest effective course given in clinical guidelines; a single dose is usually sufficient for surgical prophylaxis;

• take local susceptibility data into account in empirical therapy;

• observe hand hygiene, contact isolation and instrument sterilisation – preventing infection reduces the need for antibiotics;

• advise patients not to buy antibiotics without a prescription, not to share leftover drugs and to complete the prescribed course;

remember that vaccination (influenza, pneumococcal and others) reduces both infections and antibiotic demand.

8. Solutions

Antibiotic stewardship: increase the share of Access antibiotics and restrict over-the-counter sales [12,14].

• **Rapid diagnostics:** PCR, genomic sequencing and MALDI-TOF to identify the pathogen quickly and tailor treatment.

• **Infection prevention:** vaccination, hand hygiene, water and sanitation, hospital infection control.

• **New agents:** antimicrobial peptides, phage endolysins and AI-assisted discovery of new molecules (for example, halicin) [11].

• **One Health:** integrated monitoring of antibiotic use and resistance in humans, veterinary medicine and the environment [3,12].

• **Surveillance:** regular national collection and analysis of AMR data [3].

9. Discussion

The data presented show that AMR is a long-term threat to global health, the economy and medical safety. In this context, phage therapy offers real potential, particularly where antibiotics are running out: multidrug-resistant gram-negative infections, chronic biofilm-associated infections and cystic fibrosis. At the same time, most of the available evidence comes from case descriptions and small studies, and the results of RCTs such as PhagoBurn indicate that the technology still has to be improved [9,13]. It is therefore more accurate to regard phages not as a “miracle alternative” but as a complement to antibiotics, especially when no other option remains.

Priorities for future research include well-designed multicentre RCTs; phage banks and rapid phagogram diagnostics; quality and safety standards; adaptation of the regulatory framework; and making phage therapy affordable and accessible in low- and middle-income countries with a high AMR burden. Collecting local resistance data in each country is likewise essential for shaping appropriate treatment policy.

10. Conclusions

AMR is a global problem: GRAM forecasts more than 39 million attributable deaths in 2025–2050, and WHO GLASS 2025 shows resistance rising in many pathogen–antibiotic combinations [2,3].

• Resistance develops through enzymes, target modification, efflux, reduced permeability, biofilm and gene transfer; the principal driver is inappropriate and excessive drug use [6].

• Bacteriophage therapy is a promising direction owing to its specificity, activity against MDR strains and anti-biofilm action, but clinical evidence, standardisation and regulation remain insufficient [9,10,13].

• The most reliable path is to use phages within a comprehensive One Health strategy together with diagnostics, rational antibiotic use, prevention and new drugs.

• The most effective measures available today are rational antibiotic use (Access share ≥70%), infection prevention, rapid diagnostics and vaccination [12,14].

Declarations

Conflict of interest: the authors declare no conflict of interest.

Funding: this study received no external funding.

Author contributions: both authors contributed to the literature search, analysis and writing of the manuscript and approved the final version.

References

1. Murray CJL, Ikuta KS, Sharara F, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022;399:629–655.
2. GBD 2021 Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance 1990–2021: a systematic analysis with forecasts to 2050. Lancet. 2024;404:1199–1226.
3. World Health Organization. Global antibiotic resistance surveillance report 2025. Geneva: WHO; 2025. ISBN 9789240116337.
4. World Health Organization. WHO Bacterial Priority Pathogens List, 2024. Geneva: WHO; 2024.
5. Costerton JW, Stewart PS, Greenberg EP. Bacterial biofilms: a common cause of persistent infections. Science. 1999;284:1318–1322.
6. Aslam B, Wang W, Arshad MI, et al. Antibiotic resistance: a rundown of a global crisis. Infect Drug Resist. 2018;11:1645–1658.
7. Strathdee SA, Hatfull GF, Mutalik VK, Schooley RT. Phage therapy: from biological mechanisms to future directions. Cell. 2023;186:17–31.
8. Chan BK, Sistrom M, Wertz JE, et al. Phage selection restores antibiotic sensitivity in MDR Pseudomonas aeruginosa. Sci Rep. 2016;6:26717.
9. Jault P, Leclerc T, Jennes S, et al. Efficacy and tolerability of a cocktail of bacteriophages to treat burn wounds infected by Pseudomonas aeruginosa (PhagoBurn): a randomised, controlled, double-blind phase 1/2 trial. Lancet Infect Dis. 2019;19:35–45.
10. Ibrahim R, Aranjani JM, Kalikot Valappil V, Nair G. Unveiling the potential of bacteriophage therapy: a systematic review. Future Sci OA. 2025. doi:10.1080/20565623.2025.2468114.
11. Stokes JM, Yang K, Swanson K, et al. A deep learning approach to antibiotic discovery. Cell. 2020;180:688–702.
12. United Nations General Assembly. Political declaration of the high-level meeting on antimicrobial resistance. New York: UN; 2024.
13. Pirnay JP, Djebara S, Steurs G, et al. Personalized bacteriophage therapy outcomes for 100 consecutive cases: a multicentre, multinational, retrospective observational study. Nat Microbiol. 2024;9:1434–1453. doi:10.1038/s41564-024-01705-x.
14. World Health Organization. AWaRe classification of antibiotics for evaluation and monitoring of use, 2023. Geneva: WHO; 2023.