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BEYOND THE ANTIBIOTIC: NEW TOOLS TO CONTROL DRUG RESISTANCE IN THE POST-ANTIBIOTIC ERA

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Abstract

Antimicrobial resistance (AMR) has become one of the defining public-health challenges of the twenty-first century, and the near-total absence of genuinely novel antibiotic classes over the past three decades has forced the field to look beyond the conventional small-molecule antibiotic for solutions. This review surveys the emerging toolbox of technologies now being developed to detect, reverse, circumvent, and prevent drug resistance. Forecasts from the Global Research on Antimicrobial Resistance Project project 39 million deaths directly attributable to bacterial AMR between 2025 and 2050, a burden that conventional pipelines alone cannot address. We examine seven principal categories of new tool: engineered antimicrobial peptides; bacteriophage therapy and engineered phages; CRISPR-Cas systems repurposed as sequence-specific antimicrobials and resistance-reversal agents; nanotechnology-based delivery and intrinsically antimicrobial nanomaterials; anti-virulence and quorum-sensing interference strategies; anti-plasmid and plasmid-curing approaches; and prevention-oriented platforms including vaccines, monoclonal antibodies, and artificial-intelligence-guided stewardship and drug discovery. For each, we describe the mechanistic rationale, summarise the most recent preclinical and clinical evidence, and assess the translational barriers that stand between promising laboratory results and routine clinical use. We argue that no single tool will replace the antibiotic; rather, the future of infection control lies in a diversified, combination-based, and precision-guided portfolio in which direct-acting biologicals, resistance-reversal agents, and prevention technologies are deployed in a coordinated manner. Four diagrams and three tables integrate the quantitative and mechanistic evidence discussed throughout.

1. INTRODUCTION

The introduction of penicillin into clinical practice in the 1940s inaugurated an era in which bacterial infections that had once been routinely fatal became, for the most part, curable. For several decades the pharmaceutical industry sustained this advantage by discovering successive classes of antibiotics, each capable of overcoming the resistance that inevitably emerged to its predecessors. That virtuous cycle has now broken.

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No structurally novel class of antibiotic with activity against Gram-negative bacteria has reached the clinic in more than three decades, while resistance has continued to spread across every clinically important pathogen and every continent (Murugaiyan et al., 2022). The consequence is a growing category of infections for which no reliably effective therapy exists, and a corresponding return, in the worst cases, to the pre-antibiotic condition in which physicians can offer supportive care but not cure.

The scale of the problem has been quantified with increasing precision. The Global Research on Antimicrobial Resistance (GRAM) Project estimated that 1.27 million deaths were directly attributable to bacterial AMR in 2019, within a broader total of 4.95 million associated deaths (GBD 2021 Antimicrobial Resistance Collaborators, 2024). Its 2024 update extended these estimates forward in time and forecast that AMR will directly cause approximately 1.91 million deaths annually by 2050, a 67.5% rise on the 2021 figure, and will be associated with some 8.22 million deaths per year, so that the cumulative attributable toll between 2025 and 2050 is projected to exceed 39 million lives (GBD 2021 Antimicrobial Resistance Collaborators, 2024). The same analysis found that the burden is shifting towards older adults, with deaths among people aged 70 years and above having risen by more than 80% between 1990 and 2021, even as deaths among young children have halved. These figures are not abstract: a nationwide survey of infectious-disease specialists found that more than 60% had personally treated a patient with a pan-resistant, effectively untreatable infection within the preceding year (Kiga et al., 2020).

Crucially, the same GRAM analysis modelled the potential impact of intervention and found that the development of new antimicrobials effective against Gram-negative bacteria could avert an estimated 11.1 million deaths by 2050, while improved access to existing antibiotics and better care of infectious syndromes could avert as many as 92 million (GBD 2021 Antimicrobial Resistance Collaborators, 2024). In other words, the trajectory is not fixed, and the returns on innovation and on better use of existing tools are potentially enormous. This realisation has catalysed an unusually broad and creative research effort, one that reaches well beyond the traditional search for new small-molecule antibiotics to encompass biological agents, gene-editing systems, engineered materials, and computational platforms. The purpose of this review is to survey that effort in a structured way, to assess how close each new tool stands to clinical reality, and to consider how the tools might be combined into a coherent response to the resistance crisis.

We organise the discussion around seven categories of new tool. Three of these are direct-acting therapeutics intended to kill or inhibit pathogens by mechanisms distinct from those of conventional antibiotics: antimicrobial peptides, bacteriophages, and, in one of its modes, CRISPR-Cas. Two are resistance-reversal tools that aim not necessarily to kill the pathogen outright but to restore the efficacy of existing antibiotics by dismantling the machinery of resistance: CRISPR-Cas in its resensitising mode, and anti-plasmid and plasmid-curing strategies. Two more are precision and prevention platforms that reduce the demand for antibiotics or block resistance before it can spread: anti-virulence and quorum-sensing interference, and the combined field of vaccines, immunotherapies, stewardship, and artificial-intelligence-guided discovery. Nanotechnology cuts across these categories, functioning both as a delivery system that potentiates other agents and as a source of intrinsically antimicrobial materials. Figure 1 places the magnitude of the challenge in quantitative perspective, and Figure 2 provides a map of the toolbox that the remainder of the review examines in detail.

It is worth being explicit about why the conventional response, the discovery of new antibiotics of familiar chemical classes, has proven insufficient on its own. The economics of antibiotic development are structurally unfavourable: a successful new antibiotic is used for short courses, is deliberately reserved to slow the emergence of resistance, and therefore generates modest revenue by comparison with drugs for chronic conditions, with the result that most large pharmaceutical companies have withdrawn from the field and much of the

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remaining pipeline is sustained by small companies and public funding (Murugaiyan et al., 2022). Compounding this market failure is a scientific one: the low-hanging fruit of antibiotic discovery was largely harvested decades ago, and finding genuinely novel scaffolds that penetrate the formidable outer membrane of Gram-negative bacteria, evade their efflux pumps, and avoid cross-resistance with existing drugs has proven exceptionally difficult. The new tools reviewed here are attractive precisely because they sidestep one or both of these problems, either by exploiting mechanisms to which cross-resistance is unlikely or by addressing resistance at the level of the gene or the population rather than the individual drug-target interaction.

A further motivation for diversification is the uneven global distribution of the AMR burden. The GRAM analysis found that the impact of resistance falls disproportionately on low- and middle-income countries, where access to second-line antibiotics is limited, diagnostic infrastructure is sparse, and infection-prevention resources are stretched (GBD 2021 Antimicrobial Resistance Collaborators, 2024). Tools that are inexpensive, robust, and deployable without sophisticated laboratory support, such as certain phage preparations, rapid CRISPR-based diagnostics, and vaccines, may therefore have an outsized effect on the global burden relative to their role in high-income settings. Any assessment of the new toolbox must consider not only its scientific promise but its accessibility, since a tool that can only be deployed in a well-resourced tertiary hospital will leave the majority of the world's resistance burden untouched.

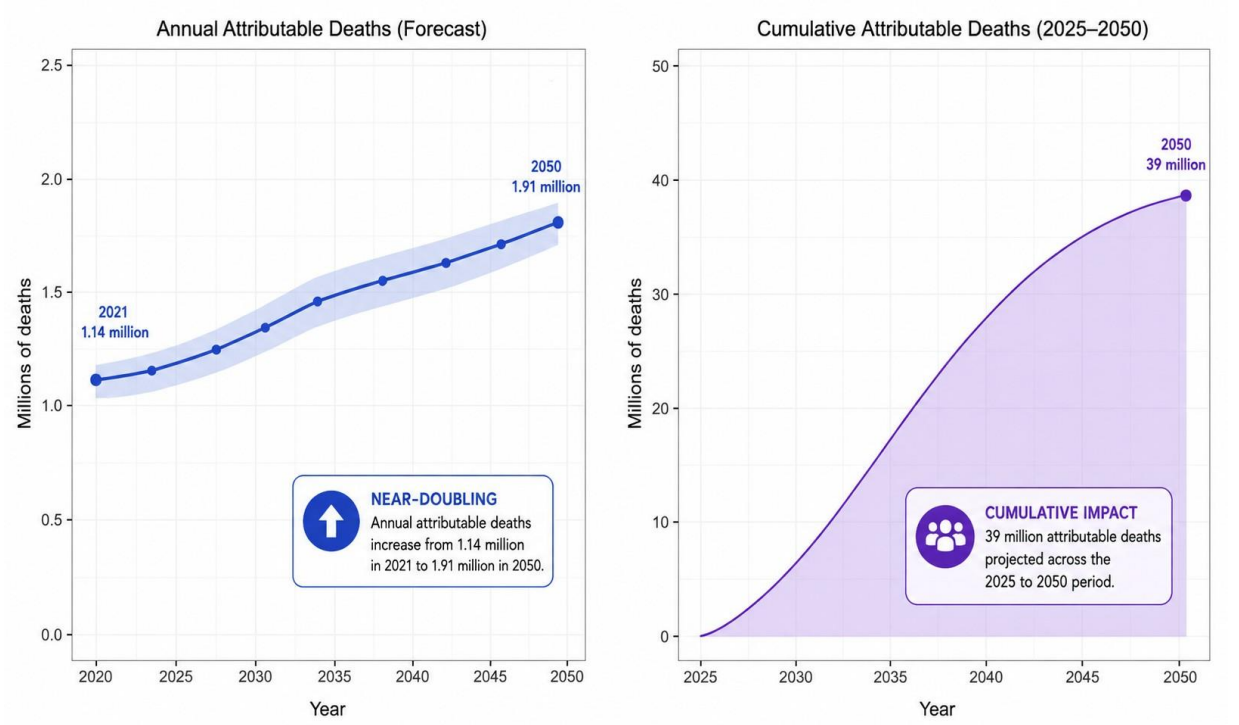


Figure 1. The global burden of antimicrobial resistance. Attributable and associated deaths for 2021 with GRAM Project forecasts to 2050, illustrating both the near-doubling of the annual attributable toll and the cumulative projection of 39 million attributable deaths across the 2025 to 2050 period. Data synthesised from the GBD 2021 Antimicrobial Resistance Collaborators (2024).

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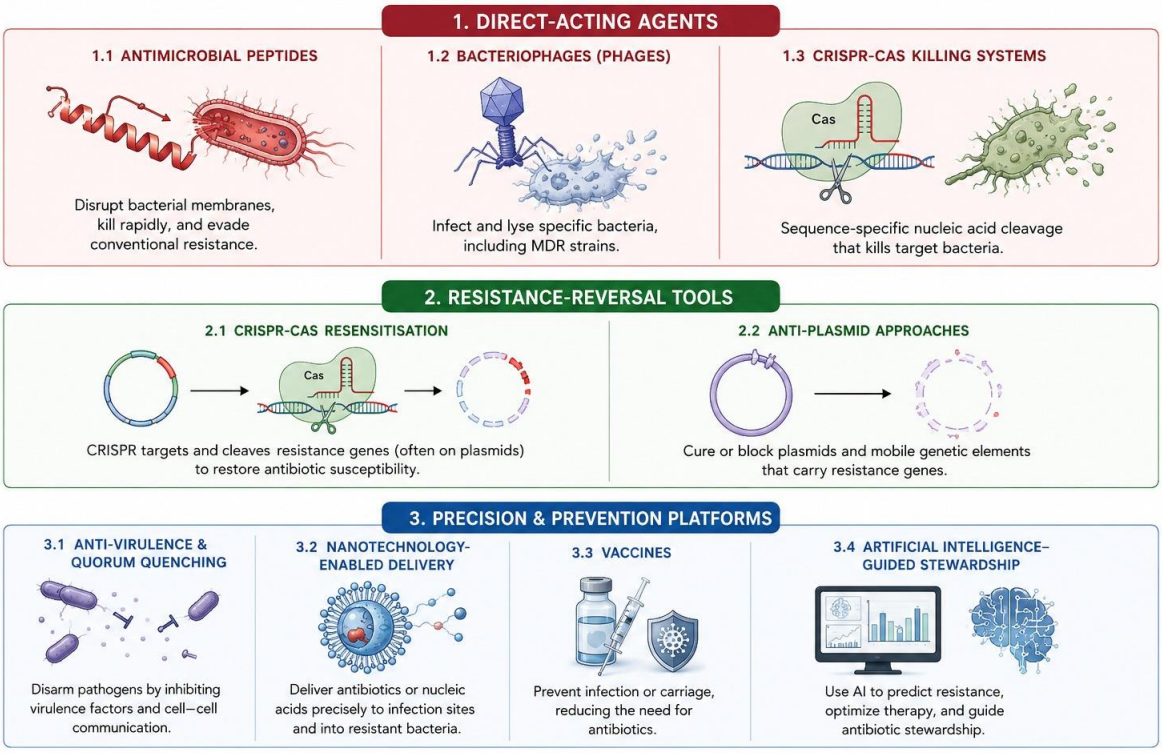


Figure 2. A taxonomy of new tools to control drug resistance. The eight domains reviewed here are grouped conceptually into direct-acting agents (antimicrobial peptides, phages, CRISPR-Cas killing), resistance-reversal tools (CRISPR resensitisation, anti-plasmid approaches), and precision or prevention platforms (anti-virulence and quorum quenching, nanotechnology-enabled delivery, vaccines, and artificial-intelligence-guided stewardship).

2. Mechanisms and Drivers of Resistance

A rational appraisal of new anti-resistance tools requires a clear understanding of the mechanisms those tools are designed to defeat. Bacterial resistance arises through a limited repertoire of biochemical strategies that recur across species. Enzymatic inactivation, exemplified by the beta-lactamases that hydrolyse the beta-lactam ring and by aminoglycoside-modifying enzymes, chemically disables the drug before it can reach its target. Target modification, such as the altered penicillin-binding protein PBP2a encoded by the mecA gene in methicillin-resistant Staphylococcus aureus or the ribosomal methylation conferred by erm genes, reduces the affinity of the drug for its binding site. Reduced permeability, achieved through the loss or downregulation of outer-membrane porins, restricts drug entry, while active efflux pumps expel drugs that do enter. Finally, target bypass allows the cell to acquire an alternative enzyme, as in the mecA and vanA systems, that performs the essential function while remaining insensitive to the antibiotic (Elshobary et al., 2025).

What makes resistance so difficult to contain is less the diversity of these mechanisms than the mobility of the genes that encode them. Antibiotic-resistance genes are frequently carried on plasmids, self-replicating extrachromosomal DNA elements that can transfer horizontally between bacteria, often across species and genus boundaries, by conjugation (Buckner, Ciusa, & Piddock, 2018). Horizontal gene transfer through conjugation, transformation, and transduction allows a resistance determinant that arises in one organism to disseminate rapidly through a bacterial community and, ultimately, around the world. The global spread of the plasmid-borne

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colistin-resistance gene mcr-1, and of numerous carbapenemase genes such as blaNDM and blaKPC, illustrates how a single mobile element can undermine an entire drug class within a few years (Banerjee et al., 2025). This mobility is precisely why several of the tools reviewed below target the plasmid or the resistance gene itself rather than the bacterial cell as a whole.

The drivers of resistance extend beyond the clinic. The excessive and often inappropriate use of antimicrobials in human medicine, in agriculture, and in animal husbandry exerts a relentless selective pressure that favours resistant organisms (Koumaki, 2025). Sub-therapeutic antibiotic use as a growth promoter in livestock, the discharge of antibiotic residues and resistance genes into the environment, and the incompleteness of infection-prevention measures in many healthcare systems all contribute to an ecosystem in which resistance genes accumulate and circulate. Any durable solution must therefore combine new therapeutic tools with measures that reduce selective pressure, a point to which the review returns in its discussion of stewardship and prevention. Table 1 summarises the principal resistance mechanisms and identifies which of the new tools is best positioned to counter each.

An important corollary of this mechanistic and ecological understanding is that resistance is best conceived as a property of microbial communities and their mobile genetic elements rather than of individual pathogenic cells. The human gut, the soil, wastewater, and the surfaces of healthcare environments all constitute reservoirs in which resistance genes persist and recombine, ready to be mobilised into pathogens when antibiotic pressure is applied. This community-level perspective explains why several of the most innovative tools reviewed here act at the level of the gene or the plasmid rather than the cell, and why prevention and stewardship, which reduce the pressure that mobilises these reservoirs, are indispensable complements to any therapeutic advance. It also clarifies why a narrow focus on killing the pathogen in front of the clinician, while necessary, is insufficient on its own to reverse the broader trajectory of resistance.

Table 1. Principal bacterial resistance mechanisms and the new tools best positioned to counter each.

Resistance mechanism	Example / genetic basis	New tool best positioned to counter it
Enzymatic inactivation	β-lactamases; carbapenemases (blaNDM, blaKPC)	CRISPR resensitisation; β-lactamase-stable AMPs; nanocarrier co-delivery
Target modification / bypass	Altered PBP2a (mecA); vanA; ribosomal methylation (erm)	CRISPR killing/resensitisation; phages; anti-virulence adjuvants
Reduced permeability	Porin loss in Gram-negatives	Membrane-active AMPs; nanoparticle penetration
Active efflux	Multidrug efflux pumps	Efflux-bypassing nanocarriers; combination therapy
Mobile resistance genes	Plasmid-borne mcr-1, blaCTX-M spread by conjugation	Anti-plasmid / plasmid curing; CRISPR plasmid cleavage; conjugation inhibitors
Biofilm tolerance / persisters	Matrix-embedded sessile communities	Quorum quenching; anti-biofilm nanoparticles; phages

3. Antimicrobial Peptides

Antimicrobial peptides (AMPs) are short, typically cationic and amphipathic molecules that form part of the innate immune defences of virtually all living organisms, from bacteria and fungi to plants, insects, and mammals. They have attracted

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intense interest as antibiotic alternatives because their principal mode of action differs fundamentally from that of conventional antibiotics. Rather than binding a single specific enzymatic target, many AMPs act physically upon the bacterial membrane, using electrostatic attraction to the negatively charged microbial surface followed by insertion into and disruption of the lipid bilayer (Aimspress review, 2025). Because this mechanism attacks a structural feature common to broad classes of bacteria and is difficult for the cell to modify without compromising membrane integrity, resistance to membrane-active AMPs tends to arise more slowly than resistance to target-specific antibiotics, and many AMPs display genuinely broad-spectrum activity.

Beyond direct membrane disruption, AMPs exhibit a valuable diversity of secondary activities. Some translocate across the membrane to interfere with intracellular targets such as DNA replication, protein synthesis, or cell-wall biosynthesis; others neutralise bacterial toxins, modulate the host immune response, or disrupt established biofilms that shield bacteria from both antibiotics and immune clearance (Murugaiyan et al., 2022). This multifunctionality makes AMPs attractive not only as stand-alone agents but as adjuvants capable of restoring the activity of conventional antibiotics against resistant organisms. Naturally occurring examples such as the defensins, cathelicidins, and the clinically used lipopeptide daptomycin illustrate the therapeutic range of the class.

The translation of AMPs into medicines has nonetheless been hampered by several persistent liabilities: susceptibility to degradation by host and bacterial proteases, potential toxicity to host cells at higher concentrations, loss of activity in the presence of physiological salt and serum, and relatively high manufacturing costs. Contemporary research is directed squarely at these problems through rational design, optimisation, and improved delivery (Aimspress review, 2025). Strategies include the substitution of D-amino acids and other non-natural residues to confer protease resistance, cyclisation and stapling to stabilise the active conformation, the design of shortened peptidomimetics that retain activity while reducing cost, and, increasingly, the use of machine-learning models trained on peptide-activity datasets to generate novel sequences with optimised potency and selectivity. Encapsulation within nanoparticles, discussed further below, can protect AMPs from degradation and target them to the site of infection while limiting systemic toxicity.

The application of computational methods to AMP design deserves particular emphasis because it represents a qualitative change in how these molecules are discovered. Where earlier work relied on isolating and testing naturally occurring peptides one at a time, generative machine-learning models can now propose entirely novel sequences predicted to combine high antibacterial potency with low haemolytic toxicity, compressing a search space of astronomical size into a tractable set of candidates for synthesis and testing. This has begun to address the historical trade-off between activity and selectivity that limited many natural AMPs, and it aligns the peptide field with the broader movement towards computationally driven antimicrobial discovery discussed later in this review. The same models can optimise secondary properties such as serum stability and salt tolerance that determine whether an active peptide can survive in the body long enough to work.

AMPs also illustrate a theme common to several new tools: the value of multifunctionality. A single engineered peptide may simultaneously permeabilise the bacterial membrane, potentiate a co-administered antibiotic by facilitating its entry, disrupt an established biofilm, and dampen the excessive host inflammatory response that contributes to tissue damage in severe infection. This convergence of antibacterial and immunomodulatory activity within one molecule is difficult to achieve with conventional antibiotics and positions AMPs as attractive components of combination regimens. Their most probable near-term clinical roles are therefore in topical and localised infections, in decolonisation of resistant carriers, and as adjuvants that restore the activity of existing antibiotics against resistant organisms, rather than as systemic monotherapies competing directly with the antibiotic class.

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The convergence of computational design and nanoscale delivery has begun to shift AMPs from an intriguing natural phenomenon towards a practical drug-development platform. Engineered AMPs now occupy an early clinical position in the translational landscape, with several candidates in trials for indications ranging from skin and soft-tissue infection to the decolonisation of resistant carriers. Their most probable near-term role is as components of combination regimens and as adjuvants that resensitise resistant bacteria to existing antibiotics, rather than as wholesale replacements for the antibiotic class.

4. Bacteriophage Therapy

Bacteriophages, the viruses that infect and replicate within bacteria, are the most abundant biological entities on Earth and were explored as antibacterial agents in the early twentieth century, before the ascendancy of antibiotics eclipsed them in Western medicine. The resistance crisis has driven a vigorous revival of interest. Phages offer a set of properties that are almost mirror-images of the weaknesses of broad-spectrum antibiotics: they are exquisitely specific, typically infecting only a narrow range of strains within a single species, which spares the beneficial microbiota that antibiotics indiscriminately damage; they are self-amplifying, multiplying at the site of infection for as long as their bacterial host is present; and they co-evolve with their targets, offering at least the possibility of countering bacterial adaptation (Dagli, Haque, & Kumar, 2024).

The clinical evidence base for phage therapy, though still maturing, has expanded considerably. A large multicentre, multinational retrospective analysis of the first 100 consecutive cases of personalised bacteriophage therapy for difficult-to-treat infections, coordinated by a Belgian consortium across 35 hospitals in 12 countries, reported clinical improvement in a substantial majority of patients when phages were used in combination with antibiotics (Pirnay et al., 2024). Importantly, that analysis documented in vitro phage-antibiotic synergy in 90% of evaluated patients and observed that phage-resistant bacterial isolates emerging during treatment frequently displayed restored antibiotic susceptibility or reduced virulence, an evolutionary trade-off that can be exploited therapeutically. A subsequent systematic review and meta-analysis identified 130 clinical studies encompassing more than 1,100 patients and distinguished non-customised, customised-selection, and customised-production approaches, finding generally favourable safety and encouraging efficacy while noting the fragmented and largely uncontrolled nature of much of the evidence (systematic review, 2025).

The central tension in the phage field is the discrepancy between the impressive results of personalised, case-by-case therapy and the inconsistent outcomes of the randomised controlled trials of fixed, non-personalised phage products conducted to date (Pirnay et al., 2024). Personalised therapy, in which phages are selected or engineered to match the patient's specific isolate, aligns naturally with the biology of phage specificity but sits awkwardly with regulatory frameworks designed for uniform, mass-produced medicines. Encouragingly, regulatory agencies in Europe, the United States, and Japan have begun to engage seriously with the development of both personalised phage therapy and pre-defined phage medicinal products, and dedicated regulatory dialogues are now under way (regulatory considerations, 2025). The Phase 2 ELIMINATE trial of a genetically enhanced six-phage cocktail for Escherichia coli urinary-tract infection provided clinical proof-of-concept for the safety and manufacturability of genetically engineered phage therapeutics, lowering translational barriers for the engineered-phage platforms discussed in the next section (CRISPR-Cas systematic review, 2026).

Several challenges remain before phage therapy can enter routine practice. Bacteria can develop resistance to phages, just as they do to antibiotics, which argues for the use of multi-phage cocktails and phage-antibiotic combinations rather than single phages. The human immune system can neutralise phages, potentially limiting the efficacy of repeated dosing. Manufacturing, characterisation, and quality control of biological products composed of self-replicating viruses raise regulatory questions distinct from those of

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chemical drugs. Among the tools reviewed here, however, phage therapy is the closest to established clinical use, already being deployed under compassionate-use and personalised-medicine frameworks in numerous countries for infections that have exhausted conventional options.

The phenomenon of phage resistance merits a more careful treatment than it often receives, because it is not simply a liability but, paradoxically, part of the therapeutic rationale. When a bacterium mutates to evade a phage, it frequently does so by altering the very surface structures, such as outer-membrane proteins, lipopolysaccharide, or efflux components, that the phage uses as receptors, and these alterations often carry a fitness cost that reduces virulence or restores sensitivity to antibiotics. This evolutionary steering, sometimes described as an evolutionary trade-off or a genetic trap, means that a pathogen escaping phage pressure may emerge weaker or resensitised rather than simply resistant, and it underlies the strong synergy observed clinically between phages and antibiotics (Pirnay et al., 2024). Rational phage-cocktail design deliberately exploits this principle by combining phages that use different receptors, so that escape from one phage does not confer escape from the others.

The distribution of phage clinical activity across pathogens reflects the priorities of the resistance crisis. Pseudomonas aeruginosa, a leading cause of healthcare-associated pneumonia and of chronic infection in cystic fibrosis and burns, features prominently in the clinical literature, as do Staphylococcus aureus in bone, joint, and prosthetic infections and Escherichia coli in urinary-tract infection. The breadth of clinical indications now under investigation, from acute pneumonia and urinary infection to chronic diabetic-foot ulcers and prosthetic-joint infections, demonstrates that phage therapy is not confined to a single niche but is being explored across the spectrum of difficult-to-treat bacterial disease. As controlled trials of both personalised and pre-defined phage products mature, and as regulatory pathways adapt to accommodate living therapeutics, phage therapy is likely to move from its current status as a treatment of last resort towards a more routine role within combination regimens.

5. CRISPR-Cas Systems as Precision Antimicrobials

Clustered regularly interspaced short palindromic repeats and their associated proteins (CRISPR-Cas) constitute an adaptive immune system that bacteria and archaea use to defend themselves against phages and foreign DNA. The same programmable, sequence-specific nucleic-acid-targeting machinery that has revolutionised genome editing can be turned against the resistant bacterium itself, and this dual capability, to kill selectively and to reverse resistance, makes CRISPR-Cas one of the most versatile new tools in the anti-resistance arsenal (Ali Agha, Al-Samydai, & Aburjai, 2025). A systematic review adhering to PRISMA methodology identified 48 eligible studies employing CRISPR-Cas9, CRISPR-Cas12a, and CRISPR-Cas3 to target an extensive list of resistance genes, including blaOXA-232, blaNDM, blaCTX-M, ermB, vanA, mecA, fosA3, blaKPC, and mcr-1, spanning resistance to carbapenems, cephalosporins, methicillin, macrolides, vancomycin, fosfomycin, and colistin (Reinvigorating AMR resilience, 2025).

CRISPR-Cas can be deployed against resistance in three broad modes, illustrated in Figure 3. In the resensitisation mode, a Cas9 nuclease is programmed to cleave a resistance-carrying plasmid or the resistance gene within the chromosome; the cell that loses the resistance determinant becomes susceptible once more to the corresponding antibiotic, so that an existing drug is effectively rescued. This approach has been used to restore fosfomycin susceptibility in E. coli and to eliminate blaKPC-2-mediated carbapenem resistance in multidrug-resistant bacteria (Reinvigorating AMR resilience, 2025). In the selective-killing mode, cleavage of an essential chromosomal target, or of a plasmid whose loss is lethal, kills the target bacterium while sparing organisms that lack the targeted sequence, offering an unprecedented degree of species- or even strain-level precision. A particularly elegant variant uses the RNA-targeting nuclease Cas13a: upon recognising a resistance-gene transcript, Cas13a

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undergoes collateral RNA cleavage that kills the cell, and because this mechanism does not depend on the physical location of the target, the CapsidCas13a construct kills bacteria even when the resistance gene resides on a plasmid, a situation in which Cas9-based systems can fail (Kiga et al., 2020).

The distinction between the DNA-targeting and RNA-targeting Cas systems is more than a technical detail, because it determines which resistance scenarios each can address. Cas9 and Cas3 cleave double-stranded DNA, which makes them well suited to destroying a chromosomal resistance gene or to curing a plasmid whose loss is not itself lethal; but when a resistance gene sits on a multi-copy plasmid, DNA cleavage may fail to kill the cell because surviving plasmid copies persist, and the outcome is resensitisation at best rather than killing. Cas13a circumvents this limitation by attacking the transcript rather than the gene and by killing through collateral cleavage of cellular RNA once activated, so that recognition of even a plasmid-borne resistance gene is lethal. The choice of Cas system is therefore dictated by the therapeutic goal, resensitisation versus killing, and by the genomic location of the target, and a mature CRISPR antimicrobial platform will likely draw on several Cas variants matched to the resistance profile at hand (Ali Agha, Al-Samydai, & Aburjai, 2025).

The third and rate-limiting dimension of CRISPR antimicrobials is delivery. A programmed Cas system is useless unless it can be introduced efficiently into the target cell, and the principal delivery vehicles under investigation are engineered bacteriophages, nanoparticles, and conjugative plasmids (CRISPR strategies review, 2024). Phage delivery couples the targeting precision of CRISPR with the natural cell-entry machinery of the phage, and the demonstration by Yosef and colleagues that CRISPR-armed temperate phages could strip resistance plasmids from pathogenic E. coli, rendering the population antibiotic-sensitive, established the feasibility of the approach. Nanoparticle delivery offers an alternative that avoids the host-range limitations of phages, while conjugative plasmids can propagate a CRISPR payload through a bacterial population by the same horizontal-transfer machinery that spreads resistance in the first place. Despite these advances, the great majority of CRISPR-Cas antimicrobial systems remain in preclinical development, and efficient, safe in vivo delivery is the chief obstacle to clinical translation (CRISPR-Cas systematic review, 2026).

CRISPR-Cas also intersects with the other tools reviewed here. CRISPR interference can be used to silence quorum-sensing genes and thereby disrupt biofilm formation in Pseudomonas aeruginosa, linking the technology to the anti-virulence strategies discussed below, and CRISPR-based diagnostics such as those built on Cas12 and Cas13 collateral cleavage provide rapid, sequence-specific detection of resistance genes that can guide precision therapy (Souto et al., 2025). The convergence of CRISPR killing, CRISPR resensitisation, and CRISPR diagnostics within a single molecular platform is one of the more striking features of the contemporary anti-resistance landscape.

The diagnostic dimension of CRISPR deserves particular attention because it addresses a bottleneck that constrains the entire field of precision antimicrobial therapy: the speed of pathogen and resistance identification. Conventional culture-based susceptibility testing takes one to several days, during which clinicians must treat empirically with broad-spectrum agents, precisely the practice that drives resistance. CRISPR-based assays exploit the collateral nucleic-acid cleavage activity of Cas12 and Cas13 to produce a detectable signal within minutes to hours of recognising a target resistance-gene sequence, offering the prospect of point-of-care detection that could narrow therapy far sooner. When such rapid diagnostics are coupled to the targeted therapeutic modes of CRISPR, the same underlying technology could in principle both identify the resistance determinant and direct an agent against it, a degree of integration without precedent in antimicrobial medicine (Ali Agha, Al-Samydai, & Aburjai, 2025).

Two caveats temper the enthusiasm for CRISPR antimicrobials. First, bacteria possess natural anti-CRISPR proteins that inhibit Cas activity, and target-site mutations can allow escape from a

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programmed guide RNA, so resistance to CRISPR-based agents is biologically plausible and must be anticipated through multiplexed targeting of several sequences at once. Second, and more importantly, the therapeutic modes of CRISPR remain overwhelmingly preclinical, held back principally by the delivery problem depicted in Figure 3, panel C. The clinical progress of engineered bacteriophage therapeutics, exemplified by the ELIMINATE trial, is significant chiefly because it validates the phage-delivery chassis on which many CRISPR antimicrobial strategies depend, thereby lowering the translational barrier for the CRISPR-armed phages that may follow (CRISPR-Cas systematic review, 2026).

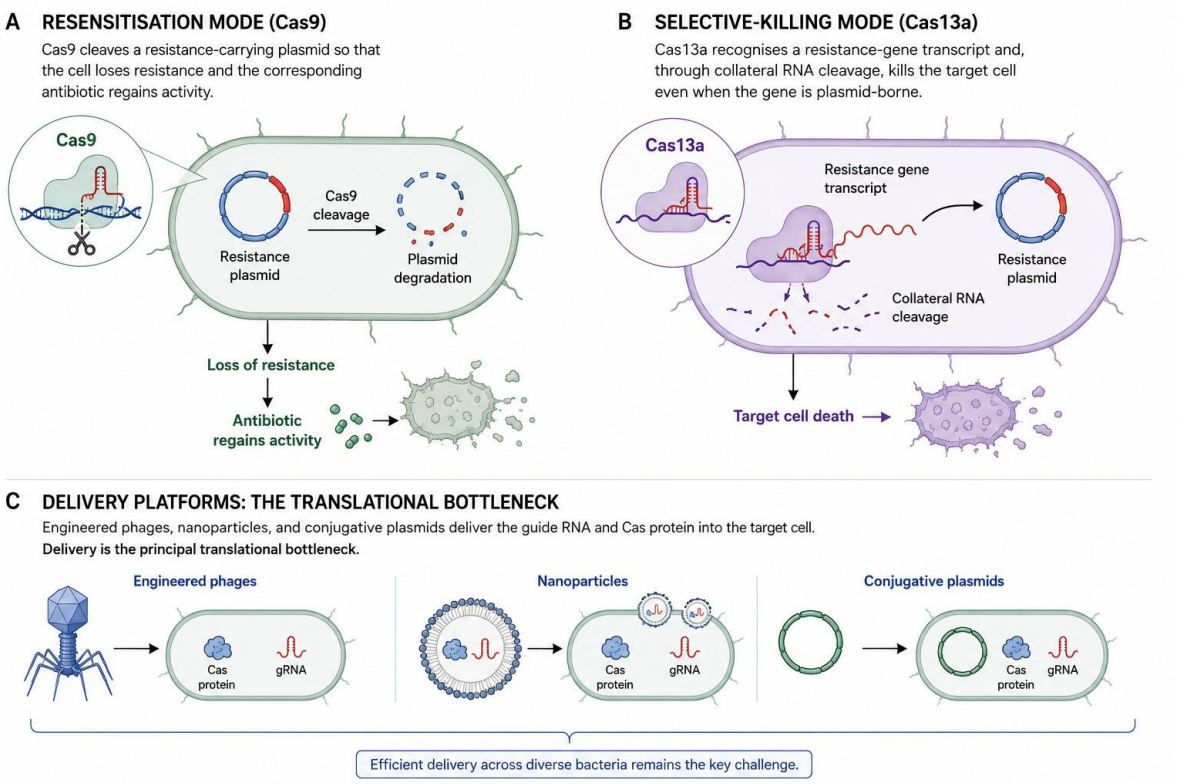


Figure 3. CRISPR-Cas as a sequence-specific antimicrobial. Panel A: in the resensitisation mode, Cas9 cleaves a resistance-carrying plasmid so that the cell loses resistance and the corresponding antibiotic regains activity. Panel B: in the selective-killing mode, Cas13a recognises a resistance-gene transcript and, through collateral RNA cleavage, kills the target cell even when the gene is plasmid-borne. Panel C: engineered phages, nanoparticles, and conjugative plasmids deliver the guide RNA and Cas protein into the target cell, delivery being the principal translational bottleneck.

6. Nanotechnology-Based Strategies

Nanotechnology occupies a distinctive position in the anti-resistance toolbox because it is less a single therapy than an enabling platform that amplifies the effectiveness of nearly every other tool while also offering antibacterial activity of its own. Operating at the scale of the bacterial cell and its membrane, nanomaterials can interact with pathogens in ways that bulk drugs cannot, penetrating biofilms, fusing with membranes, and delivering fragile cargoes intact to their targets. The following discussion separates the two principal roles of nanotechnology, delivery and direct antibacterial action, while emphasising that in practice these roles frequently combine within a single engineered system.

Nanotechnology contributes to the control of drug resistance in two complementary ways: as a

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delivery platform that enhances the performance of other antimicrobials, and as a source of nanomaterials that are themselves antibacterial. As delivery vehicles, functionalised nanoparticles can encapsulate antibiotics, antimicrobial peptides, or CRISPR payloads, protecting them from degradation, improving their solubility and pharmacokinetics, and concentrating them at the site of infection while limiting systemic exposure and toxicity (Souto et al., 2025). Because many nanocarriers can be engineered to fuse with or penetrate bacterial membranes, they can help drugs bypass the permeability barriers and efflux pumps that underlie resistance, and they can co-deliver two or more agents in fixed ratio to achieve synergy. Studies conducted between 2020 and 2025 have demonstrated antimicrobial nanocarrier systems capable of overcoming resistance in organisms including methicillin-resistant S. aureus, in some cases by delivering agents directly against mecA-bearing strains (Souto et al., 2025).

As intrinsic antimicrobials, metallic and metal-oxide nanoparticles such as silver, zinc oxide, and copper exert bactericidal effects through multiple simultaneous mechanisms, including the generation of reactive oxygen species, disruption of the cell membrane, and interference with essential enzymes and DNA. This multi-target action makes the emergence of resistance considerably less likely than for single-target antibiotics, since a bacterium would need to acquire several protective adaptations at once. Nanoparticles can also physically disrupt the extracellular matrix of biofilms, penetrating and dismantling structures that render sessile bacteria up to a thousand times less susceptible to conventional antibiotics. The versatility of the nanoscale approach, spanning delivery, direct killing, and biofilm disruption, explains why nanotechnology is best regarded not as a discrete category but as a cross-cutting enabling technology that potentiates the other tools in the arsenal.

The principal cautions surrounding antimicrobial nanomaterials concern their safety and environmental fate. The same reactive properties that make metallic nanoparticles toxic to bacteria can, at sufficient exposure, damage mammalian cells, and the long-term consequences of environmental accumulation of engineered nanoparticles are incompletely understood. These considerations place most intrinsically antimicrobial nanomaterials in the preclinical stage for systemic use, although topical and surface-coating applications, where systemic exposure is limited, are considerably more advanced. Nanocarrier delivery of approved antibiotics, by contrast, benefits from the established safety profile of its cargo and sits closer to clinical translation.

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The stimuli-responsive nanocarrier is a particularly promising refinement of the delivery concept. Such systems are engineered to release their antimicrobial cargo only in response to cues characteristic of an infection site, such as the reduced pH of an abscess, the specific enzymes secreted by a pathogen, or the presence of bacterial toxins, so that the drug is concentrated where it is needed and spared elsewhere. This targeting reduces systemic toxicity, lowers the effective dose, and limits the exposure of off-target bacterial communities, thereby diminishing the collateral selection for resistance that accompanies systemic antibiotic administration. Combined with the capacity of nanocarriers to co-deliver two agents in a fixed synergistic ratio and to shield fragile biologicals such as peptides and CRISPR payloads from degradation, these features explain why nanotechnology is increasingly regarded as the

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connective tissue of the new toolbox rather than as a standalone therapy.

7. Anti-Virulence and Quorum-Sensing Interference

A conceptually distinct approach abandons the goal of killing the pathogen altogether and instead disarms it, neutralising the virulence factors and communication systems that allow bacteria to establish infection and cause disease. The strategic appeal of anti-virulence therapy lies in the selective pressure it exerts, or rather fails to exert. Because an anti-virulence agent does not threaten bacterial survival directly, it imposes weaker selection for resistance than a conventional bactericidal antibiotic, at least in principle, and it may preserve the beneficial microbiota by targeting virulence traits specific to pathogens (Murugaiyan et al., 2022). Anti-virulence targets include toxins, adhesins that mediate attachment to host tissue, secretion systems that inject effector molecules into host cells, and the regulatory circuits that coordinate the expression of these factors.

Quorum sensing, the cell-density-dependent chemical signalling by which bacteria coordinate group behaviours, is a particularly attractive target because it governs the expression of many virulence factors and the formation of biofilms. Interfering with quorum sensing, a strategy termed quorum quenching, can prevent a bacterial population from mounting a coordinated attack even at high cell densities (Elshobary et al., 2025). Quorum quenching can be achieved by enzymes that degrade signalling molecules, by small-molecule antagonists that block signal receptors, or, as noted above, by CRISPR interference that silences the genes encoding the signalling machinery. In Pseudomonas aeruginosa, a pathogen of particular concern in cystic fibrosis and in ventilator-associated pneumonia, silencing quorum-sensing genes inhibits biofilm-matrix formation and restores susceptibility to both antibiotics and host immune clearance (Souto et al., 2025).

A conceptual attraction of quorum quenching is that, by targeting communication rather than survival, it is thought to impose comparatively weak selection for resistance, at least relative to bactericidal agents. Because a bacterium that ignores or cannot produce a quorum signal is not necessarily disadvantaged for individual growth, the evolutionary pressure to circumvent a quorum-quenching agent may be less intense than the pressure to survive a lethal antibiotic. This proposition is not absolute, since bacteria can evolve altered signalling systems and since the selective landscape depends on context, but it captures an important strategic distinction between disarming and killing. In practice, quorum-quenching and anti-virulence agents are most likely to be used as adjuvants that render pathogens more vulnerable to antibiotics and to host defences, and their development is closely intertwined with that of the biofilm-disrupting nanomaterials and CRISPR-interference tools described elsewhere in this review.

Biofilm disruption deserves emphasis in its own right, because the biofilm mode of growth is one of the most important and least tractable contributors to treatment failure. Within a biofilm, bacteria are embedded in a self-produced matrix that impedes antibiotic penetration, harbours dormant persister cells that tolerate antibiotics without being genetically resistant, and facilitates the horizontal exchange of resistance genes. Anti-virulence and quorum-quenching agents that prevent or dismantle biofilms therefore address a mechanism of tolerance that conventional antibiotics handle poorly, and they are especially promising as adjuvants that enhance the efficacy of co-administered antibiotics. The anti-virulence field remains largely in preclinical and early clinical development, and a recurring practical challenge is that disarming rather than killing a pathogen may require an intact host immune response to clear the residual infection.

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The distinction between persistence and resistance is worth drawing out, because it is frequently overlooked and because it bears directly on why anti-virulence and anti-biofilm tools are valuable. Persister cells are not genetically resistant; they are phenotypic variants that have entered a dormant, metabolically quiescent state in which the targets of most antibiotics, being active-growth processes, are simply absent. Such cells survive antibiotic exposure and can regrow once the drug is withdrawn, seeding relapse, and they are particularly abundant within biofilms. Because persistence is a physiological rather than a genetic phenomenon, it is invisible to susceptibility testing and unaddressed by drugs designed to overcome specific resistance mechanisms. Tools that dismantle biofilms, disrupt the dormant state, or disarm the virulence that allows persistent populations to cause disease therefore fill a genuine gap in the therapeutic repertoire, complementing rather than duplicating the action of both conventional antibiotics and the direct-acting new agents.

8. Anti-Plasmid and Plasmid-Curing Approaches

Because so many resistance genes are carried on plasmids, a strategy that targets the plasmid itself, rather than the bacterial cell, offers a route to reducing the prevalence of resistance across whole bacterial populations. Plasmid curing seeks to eliminate resistance plasmids from bacteria, restoring susceptibility, while anti-plasmid approaches more broadly aim to prevent plasmid replication or transfer (Buckner et al., 2018). A range of curing agents has been characterised in the laboratory, including intercalating agents and detergents, certain drugs already used in medicine such as ascorbic acid and the psychotropic chlorpromazine, and antibiotics such as the aminocoumarins, quinolones, and rifampicin, together with a variety of plant-derived compounds. Conjugation inhibitors, which block the machinery of plasmid transfer, represent a complementary tactic; examples include unsaturated fatty acids such as linoleic and oleic acids and specific small-molecule inhibitors of conjugation proteins.

More recent anti-plasmid strategies exploit the biology of the plasmid directly. Systems designed around plasmid incompatibility introduce a competing element that displaces the resistance plasmid, while CRISPR-Cas approaches, discussed above, can cleave plasmids in a sequence-specific manner to cure resistance without harming the host cell (Buckner et al., 2018). Phages and phage-delivered CRISPR systems have likewise been used to strip resistance plasmids from bacterial populations. The most significant limitation identified across this field is the scarcity of curing options suitable for use in vivo: most established curing agents are effective only under laboratory conditions and are too toxic or too non-specific for clinical use. This shortfall represents an important research gap, because an agent capable of reducing resistance-gene prevalence in the human or animal gut, or in the environment, could sensitise bacterial populations to existing antibiotics on a large scale. Even where in vivo human use is not feasible, plasmid-curing tools may help to reduce the very large reservoir of resistance genes that exists in agricultural and environmental settings.

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The anti-plasmid concept also reframes what a successful outcome might look like. Rather than curing an individual patient's infection, a population-scale anti-plasmid intervention would aim to lower the frequency of resistance genes within a microbial community, whether in a hospital ward, a livestock herd, or a wastewater system, thereby restoring the effectiveness of cheap, widely available antibiotics across many future infections at once. This is a fundamentally preventive and ecological ambition, distinct from the therapeutic aims of the direct-acting agents, and it aligns anti-plasmid strategies conceptually with stewardship and environmental management. Realising it will require agents that are safe, specific, and capable of propagating through target populations, and the engineering of conjugative delivery systems and CRISPR-armed mobile elements to meet these criteria is an active and promising area of research, albeit one that raises the ecological and biosafety questions considered later in this review.

9. Prevention, Precision, and Artificial Intelligence

The tools considered so far act after infection has occurred. An equally important set of technologies works upstream, reducing the incidence of infection, the demand for antibiotics, and the opportunity for resistance to emerge and spread. Vaccination is foremost among these. By preventing infection outright, vaccines reduce the need for antibiotic treatment and thereby lower the selective pressure that drives resistance; the GRAM analysis explicitly identified vaccine development as one of the strategies capable of averting millions of AMR-related deaths (GBD 2021 Antimicrobial Resistance Collaborators, 2024). Vaccines against resistant pathogens, and against the viral infections that frequently lead to inappropriate antibiotic prescribing, both contribute to this effect, and modelling studies suggest that expanded use of existing and pipeline vaccines could avert a meaningful fraction of the global AMR burden.

Monoclonal antibodies and other immunotherapies offer a precision alternative or complement to antibiotics, neutralising specific bacterial toxins or targeting pathogens for immune clearance without the broad microbiota disruption of conventional drugs. Alongside these biological approaches, antibiotic stewardship remains one of the most cost-effective and immediately deployable tools available. Stewardship programmes that optimise the choice, dose, and duration of antibiotic therapy reduce misuse, slow the emergence of resistance, and preserve the effectiveness of existing drugs, and evidence indicates that such programmes are crucial to maximising the useful lifespan of the current armamentarium (current approaches review, 2025). Because stewardship acts on the driver of resistance rather than on the pathogen, its benefits extend across all drug classes simultaneously.

Artificial intelligence has emerged as a powerful accelerant across several of these domains. Machine-learning models are being used to design novel antimicrobial peptides with optimised activity, to screen vast chemical libraries for compounds with antibacterial potential, to predict resistance phenotypes from bacterial genome sequences, and to guide precision prescribing by rapidly interpreting diagnostic data (Elshobary et al., 2025). Genomics-driven target discovery, in which whole-genome sequencing identifies essential bacterial genes suitable as drug targets, further exemplifies how computational and data-rich methods are reshaping antimicrobial development. When coupled with rapid, sequence-specific diagnostics such as CRISPR-based assays, these computational tools promise a future of precision antimicrobial therapy in which the pathogen and its resistance profile are identified within hours and the narrowest effective agent, whether a conventional antibiotic, a phage, or a targeted biological, is selected accordingly. Table 2 summarises representative recent evidence

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for each major category of new tool, and Figure 4 positions the categories along the discovery-to-clinic pipeline.

The predictive dimension of artificial intelligence extends beyond drug discovery into surveillance and outbreak management. Models trained on genomic and epidemiological data can forecast the emergence and spread of resistant clones, flag the appearance of novel resistance determinants, and identify the environmental and prescribing patterns that select for resistance, enabling pre-emptive intervention rather than reactive response. Coupled to the increasingly affordable sequencing of clinical and environmental isolates, such systems could transform AMR from a phenomenon detected only after it has caused harm into one anticipated and contained. The realisation of this potential depends, however, on the quality and representativeness of the training data, and models built predominantly on data from high-income settings may generalise poorly to the low- and middle-income regions where the burden is greatest, echoing a limitation that recurs throughout medical artificial intelligence.

It is important to situate these high-technology approaches alongside the decidedly low-technology measures that remain among the most effective of all. Basic infection prevention and control, including hand hygiene, sanitation, clean water, and safe surgical practice, prevents the transmission of resistant organisms and reduces the need for antibiotics at a fraction of the cost of any novel therapeutic. The GRAM modelling that projected 92 million deaths avertable through better care and access, more than eight times the number avertable through new Gram-negative antibiotics alone, is a forceful reminder that innovation and implementation are complements rather than substitutes (GBD 2021 Antimicrobial Resistance Collaborators, 2024). A balanced anti-resistance strategy must therefore invest simultaneously in the frontier tools reviewed here and in the unglamorous but highly effective work of prevention, stewardship, and equitable access to existing medicines.

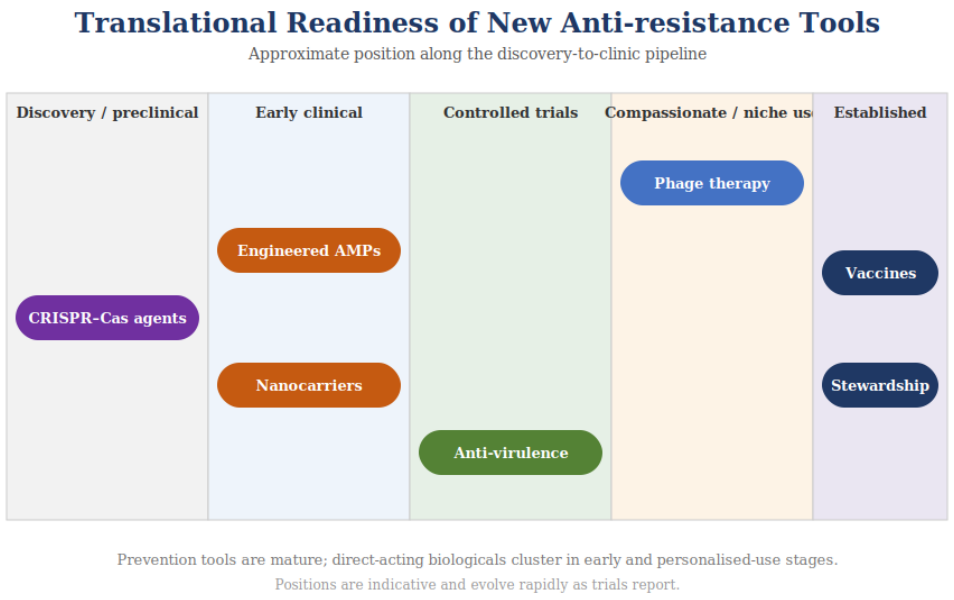


Figure 4. Translational readiness of new anti-resistance tools. The categories reviewed here occupy different positions along the discovery-to-clinic pipeline: prevention-oriented platforms such as vaccines and stewardship are mature and established, phage therapy is in controlled trials and widespread personalised or compassionate use, engineered antimicrobial peptides and nanocarriers are in early clinical development, and CRISPR-Cas antimicrobials remain largely preclinical. Positions are indicative and evolve rapidly as new trial data emerge.

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Table 2. Representative recent evidence for each major category of new anti-resistance tool.

Tool category	Representative recent evidence	Key source
Antimicrobial peptides	Rational design, D-amino-acid substitution, and nano-delivery to improve stability and reduce toxicity	Murugaiyan et al. (2022)
Bacteriophage therapy	100 consecutive personalised cases; phage-antibiotic synergy in 90% of evaluated patients; resistance trade-offs	Pirnay et al. (2024)
CRISPR-Cas antimicrobials	48 studies targeting mecA, mcr-1, blaKPC and others; CapsidCas13a kills plasmid-borne targets	Kiga et al. (2020); Reinvigorating AMR resilience (2025)
Nanotechnology	Functionalised nanocarriers overcoming resistance in MRSA (2020-2025)	Souto et al. (2025)
Anti-virulence / quorum quenching	CRISPRi silencing of quorum-sensing genes inhibits P. aeruginosa biofilm matrix	Souto et al. (2025); Elshobary et al. (2025)
Anti-plasmid / curing	Conjugation inhibitors and CRISPR plasmid cleavage; lack of in vivo options	Buckner et al. (2018)
Prevention & AI	Vaccination and Gram-negative drug development could avert 11-92 million deaths by 2050	GBD 2021 AMR Collaborators (2024)

10. Combination Strategies and Integration

A recurring theme across every category reviewed here is that no single new tool is likely to replace the antibiotic, and that the greatest promise lies in combination. The biology of resistance itself argues for this conclusion: a bacterial population challenged simultaneously by two agents with independent mechanisms must acquire two distinct adaptations to survive, an event exponentially less probable than the acquisition of either alone. This logic underlies the observed synergy between phages and antibiotics, in which phage-resistant mutants frequently pay a fitness cost that restores antibiotic susceptibility or reduces virulence, so that the two agents together corner the pathogen evolutionarily in a way neither could alone (Pirnay et al., 2024). Similar synergies have been documented between antimicrobial peptides and conventional antibiotics, and between nanocarrier-delivered drug combinations.

The tools also combine at the level of mechanism rather than merely of co-administration. CRISPR-Cas can be delivered by engineered phages, so that phage specificity and CRISPR programmability reinforce one another; nanoparticles can deliver CRISPR payloads or antimicrobial peptides, protecting them and targeting them precisely; anti-virulence and quorum-quenching agents can be paired with antibiotics or immune-based therapies to disarm and then clear a pathogen; and CRISPR interference can silence the quorum-sensing circuits that anti-virulence strategies target. This modular interoperability suggests that the future anti-resistance toolbox will not be a set of competing alternatives but an integrated system whose components are assembled to fit the pathogen, the site of infection, and the resistance profile of the individual case. Table 3 sets out the principal advantages, limitations, and translational status of each tool to support such rational combination.

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Table 3. Comparative advantages, limitations, and translational readiness of the new tools.

Tool	Advantages	Limitations	Readiness
Antimicrobial peptides	Broad spectrum; membrane-active; low resistance; immunomodulatory	Protease degradation; toxicity; cost	Early clinical
Bacteriophages	Highly specific; self-amplifying; microbiota-sparing; synergy with antibiotics	Phage resistance; immune neutralisation; regulatory fit	Trials / personalised use
CRISPR-Cas	Sequence-specific killing and resensitisation; programmable	In vivo delivery; anti-CRISPR resistance	Mostly preclinical
Nanotechnology	Delivery, direct killing, biofilm disruption; multi-target	Host toxicity; environmental fate	Preclinical / topical
Anti-virulence / QQ	Weak resistance pressure; microbiota-sparing; anti-biofilm	Needs intact host immunity; narrow	Early development
Anti-plasmid	Reduces resistance-gene prevalence at population scale	Few in vivo-usable agents	Preclinical
Vaccines / stewardship / AI	Prevent infection; reduce demand; cross-class benefit	Coverage gaps; behaviour change	Established / expanding

The tools also combine at the level of mechanism rather than merely of co-administration. CRISPR-Cas can be delivered by engineered phages, so that phage specificity and CRISPR programmability reinforce one another; nanoparticles can deliver CRISPR payloads or antimicrobial peptides, protecting them and targeting them precisely; anti-virulence and quorum-quenching agents can be paired with antibiotics or immune-based therapies to disarm and then clear a pathogen; and CRISPR interference can silence the quorum-sensing circuits that anti-virulence strategies target. This modular interoperability suggests that the future anti-resistance toolbox will not be a set of competing alternatives but an integrated system whose components are assembled to fit the pathogen, the site of infection, and the resistance profile of the individual case. Table 3 sets out the principal advantages, limitations, and translational status of each tool to support such rational combination.

Combination also offers a strategy for managing the resistance that will inevitably arise to the new tools themselves. Just as the co-administration of multiple antibiotics with independent mechanisms has long been used to suppress the emergence of resistance in tuberculosis and HIV, the deliberate pairing of, for example, a phage cocktail with an antibiotic, or an antimicrobial peptide with a conventional drug, raises the genetic barrier to escape and can steer bacterial evolution towards less dangerous phenotypes. The evolutionary trade-offs documented in phage therapy, where escape from the phage restores antibiotic sensitivity, are the clearest example of a combination that turns the pathogen's own adaptive response against it. Designing such collaterally constraining combinations rationally, informed by an understanding of the fitness costs and cross-sensitivities involved, is likely to become a central discipline within antimicrobial therapeutics, and it is one in which computational modelling of bacterial evolution will play an increasingly important part.

11. Challenges and Limitations

Considerable obstacles stand between the promise surveyed here and its realisation in routine care. Delivery is the most pervasive technical challenge: antimicrobial peptides are degraded by proteases,

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CRISPR systems must be introduced efficiently into target cells within the complex environment of an infection, and nanocarriers must reach the site of infection without provoking toxicity. For the biological agents in particular, delivery to intracellular pathogens and across biofilm matrices remains only partially solved. Resistance to the new tools themselves is a second concern that must not be underestimated: bacteria can evolve resistance to phages, to antimicrobial peptides, and, through anti-CRISPR proteins and target-site mutation, to CRISPR-Cas systems, so that the durability of any single tool cannot be assumed.

Regulatory and manufacturing frameworks present a third category of difficulty. Living, self-replicating therapeutics such as phages, personalised products tailored to an individual patient's isolate, and gene-editing agents do not fit comfortably within regulatory systems designed for uniform chemical drugs, and the tension between personalised efficacy and standardised approval, most visible in the phage field, must be resolved for these therapies to scale (regulatory considerations, 2025). Manufacturing biological products to consistent quality, characterising them adequately, and ensuring their stability all add complexity and cost. Economic barriers compound these problems: the return on investment for a new antimicrobial used sparingly and for short courses is poor by comparison with drugs for chronic disease, and this market failure has contributed to the withdrawal of major pharmaceutical companies from antibacterial research, a disincentive that applies with equal force to several of the new modalities.

Finally, safety and ecological considerations require careful attention. Antimicrobial nanomaterials may harm host cells and accumulate in the environment; the widespread release of CRISPR-based agents or conjugative anti-plasmid systems into microbial ecosystems raises questions about unintended gene flow; and any tool that exerts selective pressure, however novel its mechanism, will eventually be met by bacterial adaptation. Responsible development therefore demands that new tools be evaluated not only for their efficacy against the target pathogen but for their effects on the wider microbial community and environment, and that they be deployed within a framework of stewardship that preserves their effectiveness.

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A further, often underappreciated challenge concerns the clinical trial designs and evidentiary standards appropriate to these novel modalities. The randomised controlled trial, the gold standard for conventional drugs, sits uneasily with therapies that are personalised to the individual patient's isolate, as much phage and CRISPR therapy is intended to be, because the intervention differs from patient to patient. Novel trial frameworks, including adaptive designs, personalised-medicine registries, and rigorous observational cohorts with clearly defined outcomes, will be needed to generate credible evidence without forcing inherently individualised therapies into a one-size-fits-all mould. The inconsistency between the encouraging results of personalised phage case series and the disappointing outcomes of fixed-product randomised trials is a direct manifestation of this methodological tension, and resolving it is as much a regulatory and statistical problem as a scientific one (Pirnay et al., 2024; regulatory considerations, 2025).

12. Future Perspectives

The trajectory of the field points towards a model of infection control that is diversified, precise, and combination-based. In place of the twentieth-

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century paradigm of a small number of broad-spectrum antibiotics deployed empirically, the emerging paradigm envisions rapid, sequence-specific diagnosis of the pathogen and its resistance profile, followed by the selection of the narrowest effective intervention from a broad portfolio of tools, be it a conventional antibiotic, a tailored phage cocktail, a CRISPR resensitising agent, an anti-virulence adjuvant, or a combination assembled to fit the case. Artificial intelligence and genomics will underpin both the diagnosis and the selection, and will accelerate the discovery and optimisation of the agents themselves (Elshobary et al., 2025).

Realising this vision will require sustained investment, regulatory innovation, and interdisciplinary collaboration among microbiologists, engineers, clinicians, computational scientists, and the pharmaceutical industry. It will also require that prevention, through vaccination, infection control, and stewardship, be treated as an equal partner to therapeutic innovation rather than an afterthought, since the GRAM modelling makes clear that better use of existing tools could avert several times more deaths than new drugs alone (GBD 2021 Antimicrobial Resistance Collaborators, 2024). The convergence of these therapeutic and preventive strands, supported by precision diagnostics and computational design, offers a credible path away from the post-antibiotic future that current trends portend.

Equity must be a central design criterion rather than a downstream consideration. Because the burden of resistance falls most heavily on low- and middle-income countries, tools developed only for well-resourced hospitals will do little to change the global trajectory. Priority should therefore be given to modalities that are affordable, stable without cold-chain logistics, and deployable with limited laboratory infrastructure, and to the strengthening of local capacity for diagnosis, surveillance, and manufacturing. Phage preparations that can be produced regionally, vaccines that prevent infection before it requires treatment, rapid diagnostics that can be run at the point of care, and stewardship programmes adapted to local prescribing realities all have the potential to deliver disproportionate benefit in exactly the settings where the need is greatest. A future in which advanced anti-resistance tools are available only to the few would represent a scientific success but a public-health failure, and avoiding that outcome is as much a matter of policy, financing, and global cooperation as of laboratory innovation.

13. Conclusion

Antimicrobial resistance is a slow-moving but relentless crisis whose projected toll of 39 million attributable deaths between 2025 and 2050 demands a response commensurate with its scale. The decades-long drought in novel antibiotic classes has compelled the field to look beyond the conventional antibiotic, and the result is an unusually rich and creative toolbox: engineered antimicrobial peptides that disrupt membranes and resist degradation; bacteriophages, increasingly engineered and now supported by a growing clinical evidence base; CRISPR-Cas systems that can kill resistant bacteria selectively or reverse resistance by dismantling the genes that encode it; nanotechnologies that deliver, potentiate, and directly kill; anti-virulence and quorum-quenching strategies that disarm rather than destroy; anti-plasmid approaches that attack the mobile elements at the heart of resistance dissemination; and prevention platforms, from vaccines to stewardship to artificial-intelligence-guided discovery, that reduce the demand for antibiotics in the first place. None of these tools is a panacea, and each faces real barriers of delivery, resistance, regulation, economics, and safety. Their collective promise, however, lies precisely in their diversity and their capacity for combination. The most probable and most hopeful future is not one in which a single successor to the antibiotic emerges, but one in which a coordinated, precision-guided portfolio of complementary tools is deployed intelligently against each pathogen, restoring to medicine the ability to treat bacterial infection that the resistance crisis has begun to erode.

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