

REVIEW ARTICLE

Vaccines and non-antibiotic therapeutics for combating antimicrobial resistance: From prevention to precision interventions

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Abstract

Antimicrobial resistance (AMR) poses an escalating threat to global health by compromising the effectiveness of conventional antibiotics and increasing the risk of treatment failure for common infections. As the development of new antibiotics lags behind the rapid emergence of resistant pathogens, alternative strategies are urgently needed to sustain effective infection management. Vaccines and non-antibiotic therapeutics represent complementary approaches that can reduce reliance on conventional antimicrobials while limiting the selective pressures that drive resistance. While vaccinations prevent infections, reduce pathogen transmission, and decrease antibiotic consumption at both individual and population levels, precision therapeutics, in parallel, enable targeted treatment of resistant infections while preserving host microbial ecology. This review synthesizes current evidence on the role of vaccines as underutilized tools for AMR mitigation and examines emerging non-antibiotic therapeutic strategies with translational and clinical potential. Beyond individual modalities, we propose an integrated framework that combines prevention, precision interventions, stewardship, and surveillance to enhance AMR control. Key considerations include research priorities, regulatory pathways, implementation challenges, and equitable access across diverse healthcare settings. By shifting from a predominantly antibiotic-centered approach toward prevention and targeted biologic interventions, these strategies offer a sustainable pathway to reduce the burden of AMR and preserve the effectiveness of existing therapies.

Keywords: Antimicrobial resistance; Vaccines; Non-antibiotic therapeutics; Precision medicine; Global health

1. Introduction

Antimicrobial resistance (AMR) has emerged as a critical and rapidly escalating global health threat that compromises the effective treatment of infectious diseases and threatens the foundations of modern medicine. In 2019, AMR was directly responsible for approximately 1.27 million deaths and contributed to nearly 4.95 million deaths worldwide, thereby emphasizing its profound impact on human health.¹ The principal determinants of AMR include the misuse and overutilization of antimicrobials in human healthcare, veterinary practices, and agriculture, which facilitate the evolution and dissemination of drug-resistant pathogens.² Without sustained global action, the burden of AMR is projected to escalate considerably. Prior analyses have predicted that, if current trends continue, up to 10 million deaths annually could occur by 2050 due to drug-resistant infections, surpassing many of the leading global causes of mortality.³ Recent modeling also indicates that antibiotic-resistant bacterial infections could lead to tens of millions of deaths over the coming decades, with significant healthcare and economic implications if current containment strategies are not enhanced.⁴

Concurrently, the antibiotic development pipeline has stagnated due to scientific, regulatory, and economic challenges, with only a limited number of novel drugs reaching the market. Many of these belong to existing classes that provide minimal benefit against emerging resistance mechanisms.² This expanding disparity between escalating resistance and restrained therapeutic development underscores the critical necessity for alternative strategies beyond conventional antibiotics. Vaccines, recognized as one of the most significant public health interventions in history, present a strategic yet underexplored approach to combat AMR. By preventing infections, reducing pathogen transmission, and decreasing overall antibiotic use, vaccines diminish the selective pressure that fosters resistance development and interrupt key amplification pathways within the AMR cycle (Figure 1).⁵

Studies have shown that vaccination programs targeting *Streptococcus pneumoniae*, *Haemophilus influenzae*, and influenza reduce disease burden and antibiotic prescription rates, thereby lowering the potential for resistance development.^{6,7} Despite these successes, many high-priority drug-resistant pathogens, e.g., *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Staphylococcus aureus*, and drug-resistant *Escherichia coli*, lack effective vaccines, even though they contribute disproportionately to healthcare-associated infections and AMR mortality.⁸

Emerging waves of non-antibiotic therapeutics, including bacteriophages, monoclonal antibodies (Mabs),

clustered regularly interspaced short palindromic repeats (CRISPR)-based antimicrobials, anti-virulence agents, and microbiome-directed therapies, are recognized as promising complements or alternatives to small-molecule antibiotics.⁹ Nevertheless, the persistent global burden of AMR hampers the dissemination and effectiveness of these innovations, as many approaches are still in early clinical development or face limited accessibility due to various economic, regulatory, and infrastructural challenges that restrict their implementation, particularly in resource-limited settings.^{2,4} Furthermore, the adaptive capacity of microbial populations facilitates the continual emergence of resistance, even against newly developed interventions, thereby reinforcing the limitations of relying solely on therapeutic innovation.²

This review examines the strategic potential of vaccines and innovative therapeutics in addressing AMR. It explores the biological mechanisms through which vaccines can mitigate resistance, reviews evidence from existing and emerging vaccine platforms, summarizes novel non-antibiotic approaches, and proposes an integrated framework for incorporating these tools into global AMR action plans. By shifting the focus from reactive antibiotic treatment toward prevention and biologically targeted interventions, this paradigm aims to deliver sustainable, long-term solutions to one of the most significant challenges in global health.

2. Vaccines as tools for antimicrobial resistance mitigation

Vaccines are among the most effective yet underutilized interventions for mitigating AMR. Unlike antibiotics, which are administered after infection has occurred and exert strong selective pressure on microbial populations, vaccines primarily function through preventive measures. By decreasing infection incidence, limiting pathogen transmission, and reducing dependence on antimicrobial therapy, vaccines both directly and indirectly interfere with the evolutionary and epidemiological processes that facilitate the emergence and dissemination of resistance.^{10,11} Importantly, the influence of vaccines on AMR extends beyond individual protection to include population-level effects through herd immunity, thereby establishing immunization as a fundamental component of sustainable resistance management strategies.^{5,12}

2.1. Biological mechanisms linking vaccines and antimicrobial-resistance reduction

Vaccines stimulate host immune responses that enable rapid recognition and elimination of specific pathogens. Through multiple interconnected biological pathways,

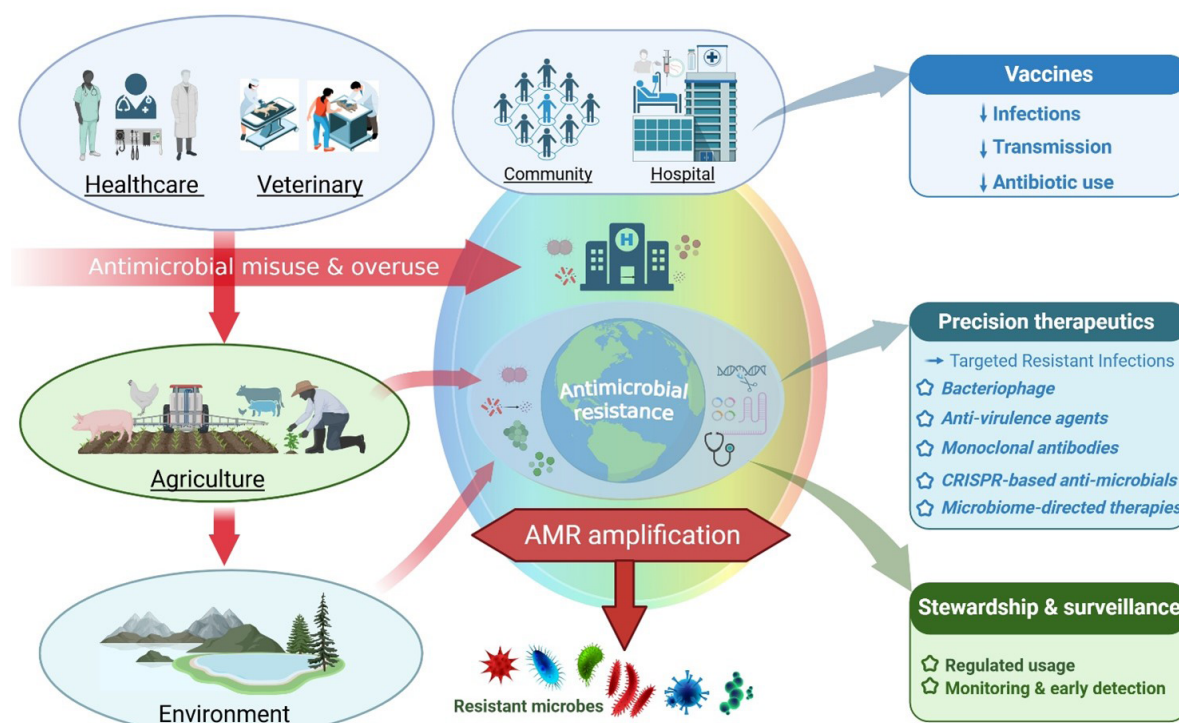


Figure 1. Determinants of antimicrobial resistance (AMR) and key intervention points across the One Health continuum. Schematic obtained from BioRender with permission; created by Suleiman, A. (2026) <https://BioRender.com/0x8fevc>.

vaccination contributes to AMR mitigation by reducing infection burden, lowering antibiotic use, preventing secondary infections, and diminishing selective pressure for resistance development (Figure 2).¹¹

2.1.1. Reducing infections

The most direct mechanism through which vaccines mitigate AMR is by decreasing the overall incidence of infectious diseases. A lower number of infections results in fewer clinical encounters requiring antimicrobial therapy, thereby diminishing both appropriate and inappropriate antibiotic use.¹¹ At the population level, this reduction in disease burden limits the opportunities for resistant strains to develop, persist, and disseminate.

2.1.2. Lowering antibiotic use

Vaccines protect not only those who are vaccinated but also unvaccinated people through herd immunity. By disrupting chains of pathogen transmission, vaccination significantly reduces antibiotic use in communities.¹¹ This phenomenon has been empirically validated by Gianacas *et al.*¹², who documented a noteworthy decrease in antibiotic prescriptions among vaccinated individuals. Reducing

antibiotic exposure mitigates selective pressures that promote the emergence of resistant organisms, thereby yielding enduring benefits at the population level.

2.1.3. Preventing secondary infections

Vaccination against primary infections diminishes the likelihood of secondary bacterial infections, which frequently require antibiotic treatment. Influenza vaccines serve as an example by preventing influenza infections and consequently reducing the risk of secondary complications, such as pneumonia and otitis media.¹³ Additionally, prelicensure studies of pneumococcal conjugate vaccines conducted in Africa demonstrated a 67% reduction in penicillin-resistant invasive pneumococcal disease among vaccinated populations compared with control groups.¹⁴ By interrupting infection cascades, vaccines effectively decrease downstream antimicrobial consumption and the subsequent development of resistance.

2.1.4. Reducing selective pressure

Selective pressure emerges when the utilization of antimicrobials preferentially supports the survival and proliferation of resistant microorganisms. Vaccines

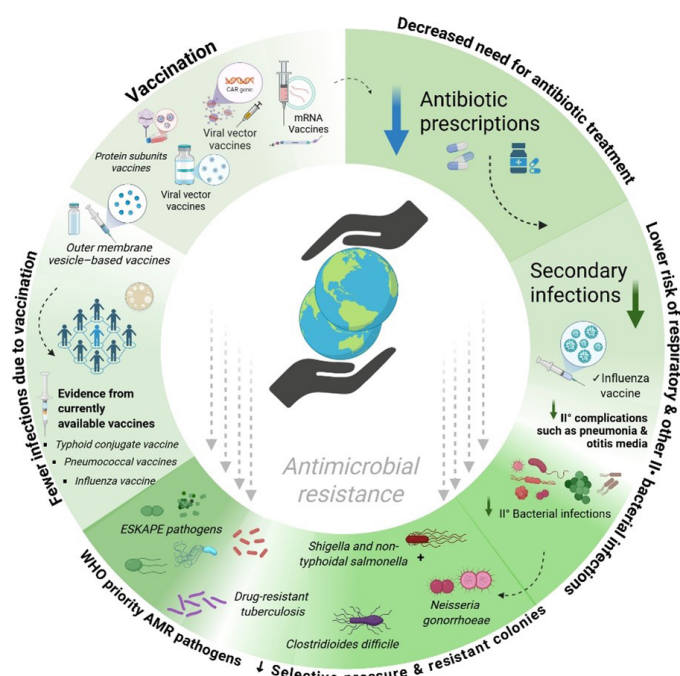


Figure 2. Biological mechanisms by which vaccines contribute to antimicrobial-resistance mitigation. Schematic obtained from BioRender with permission; created by Suleiman, A. (2026) <https://BioRender.com/7p2bipg>.

mitigate this selective pressure by reducing the overall incidence of infections and, consequently, the necessity for antimicrobial therapy.¹⁰ Unlike antibiotics, vaccines function preemptively, before substantial pathogen populations are established, and stimulate immune responses against multiple antigens, reducing the likelihood of resistance development and its benefits.¹⁵

2.2. Evidence from currently available vaccines

2.2.1. *Pneumococcal vaccines*

Pneumococcal vaccines have demonstrated considerable success in reducing invasive pneumococcal disease and antibiotic resistance across both vaccinated and unvaccinated populations through herd immunity.¹⁶ The deployment of pneumococcal conjugate vaccines, such as PCV13, PCV15, and PCV20, in adult populations has resulted in significant reductions in hospitalizations, outpatient visits, and antibiotic prescriptions, underscoring their substantial public health and AMR-mitigating benefits in high-income settings.¹⁶

2.2.2. *Haemophilus influenzae type b vaccine*

Before the widespread implementation of *Haemophilus influenzae* type b (Hib) vaccination, global surveillance data indicated that a considerable proportion of Hib strains

were beta-lactamase-positive, with notable geographic variation.¹⁷ This resistance landscape underwent a significant transformation following the introduction of routine Hib conjugate vaccination. The incidence of the disease declined markedly, accompanied by a substantial reduction in beta-lactamase-producing strains, thereby underscoring the vaccine's effectiveness in both disease control and the modulation of resistance dynamics.^{13,17}

2.2.3. *Influenza vaccine*

Although influenza vaccines do not directly target bacterial pathogens, they still contribute significantly to AMR mitigation. During influenza seasons, a substantial proportion of antibiotic prescriptions are unnecessary, thereby contributing to the selection of antibiotic resistance in both community and hospital settings.¹⁸ Influenza vaccination has been linked to reduced outpatient antibiotic prescribing, decreased antibiotic utilization in long-term care facilities, and a decline in hospital admissions for pneumonia.¹⁹

2.2.4. *Typhoid conjugate vaccine*

Typhoid fever remains a significant public health issue in regions with inadequate water and sanitation infrastructure. Typhoid conjugate vaccines offer long-lasting immunity and robust protection against multidrug-resistant and

extensively drug-resistant *Salmonella enterica* serovar Typhi strains.²⁰ In Pakistan, where extensively drug-resistant typhoid was identified in 2016, the deployment of typhoid conjugate vaccines has resulted in a substantial reduction in resistant typhoid cases, exemplifying the vaccine's effectiveness in mitigating AMR within endemic areas.²¹

2.2.5. Meningococcal vaccine

The evolution of novel meningococcal vaccines and the effective implementation of targeted vaccination programs have led to a substantial decrease in the burden of meningococcal disease worldwide, representing a major public health accomplishment.²² The advent of the polysaccharide meningococcal vaccine and the subsequent introduction of the meningococcal conjugate vaccine have led to dramatic reductions in meningococcal disease incidence by providing both individual and herd immunity.^{23,24} The effectiveness of these vaccines contributes to reduced antibiotic use and AMR.²⁵

2.2.6. Pertussis vaccine

A single dose of the Tdap (diphtheria, tetanus, and pertussis) vaccine administered late in pregnancy protects infants during their initial months of life before the start of their standard vaccination regimen.²⁶ The implementation of vaccination programs in the United Kingdom and the United States resulted in substantial decreases in newborn hospitalizations and fatalities attributed to pertussis, with vaccine efficacy estimated between 70% and 95% against infant pertussis and even higher against severe outcomes.²⁷ Maternal Tdap reduces the necessity for therapeutic macrolide administration in index patients and post-exposure prophylaxis for close contacts by preventing neonatal disease. Tdap during pregnancy also boosts maternal immunity against tetanus and diphtheria. Maternal antibodies may offer additional neonatal protection against diphtheria where transmission persists, and against tetanus, which would otherwise prompt adjunctive antimicrobial treatment, achieving elimination in most priority countries.⁷

2.3. Vaccine development for the World Health Organization's priority antimicrobial-resistance pathogens

2.3.1. ESKAPE pathogens

The ESKAPE (*Enterococcus faecium*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter spp*) persist as major drivers of multidrug-resistant infections, particularly in healthcare settings.²⁸ Their adaptability, ability to disseminate resistant clones,

and capacity to evade host immunity present considerable obstacles for vaccine development. The development of vaccines targeting ESKAPE pathogens presents numerous challenges, including the difficulty in assessing vaccine efficacy attributable to the low incidence of infection within the general population; the compromised immune systems of target populations, resulting from the severity of infections, complicate the establishment of critical endpoints; and, challenges in identifying immunogenic targets across species and in evading the host immune responses.^{29,30} Despite these challenges, progress continues to be achieved. The tetravalent bioconjugate vaccine candidate Kleb4V is the inaugural *K. pneumoniae* vaccine to undergo clinical assessment, demonstrating satisfactory safety and immunogenicity in adults aged 55–70 years.³¹

2.3.2. Gonorrhea

Neisseria gonorrhoeae has developed resistance to multiple antimicrobial classes, significantly constraining treatment options. The development of a vaccine has been impeded by antigenic diversity and the absence of protective immunity following natural infection.³² Nevertheless, owing to shared virulence factors between gonococci and meningococci, outer membrane vesicle (OMV)-based meningococcal vaccines, such as MenB-4C and MenNZB, have demonstrated partial cross-protection against gonorrhea. MenB-4C has been associated with a 30–40% reduction in prevalence, while modeling studies indicate that even modest vaccine efficacy could produce substantial population-level impacts.^{32,33}

2.3.3. Drug-resistant tuberculosis

Although the Bacille Calmette–Guérin (BCG) vaccine protects against severe manifestations of tuberculosis (TB) in pediatric populations, its effectiveness against adult pulmonary disease remains limited. Mathematical modeling suggests that a vaccine with 50% efficacy could reduce fatalities associated with rifampicin-resistant TB by over 7%.³⁴ Presently, vaccine development efforts include BCG replacement vaccines, booster formulations, and vaccines aimed at latent infections. Currently, 15 TB vaccine candidates are undergoing clinical evaluation across various platforms, including viral vectors, recombinant protein subunits, live mycobacterial vaccines, and nucleic acid-based strategies.³⁵

2.3.4. Shigella and non-typhoidal Salmonella

The antigenic heterogeneity of *Shigella* complicates vaccine development, necessitating multivalent formulations. Currently, licensed vaccines are limited geographically, though multiple killed, live-attenuated, and subunit candidates are in clinical trials.³⁶ For non-typhoidal

Salmonella (NTS), combination vaccine strategies have been proposed to address logistical and economic challenges. One such approach involves a combined invasive NTS–*Shigella* vaccine, although combination vaccines introduce additional complexity and cost.³⁷ Clinical evaluation of the iNTS-GMMA vaccine has demonstrated acceptable safety and progression to advanced development stages.³⁸

2.3.5. *Clostridioides difficile*

Vaccination against *Clostridioides difficile* offers the potential to protect both vaccinated individuals and their contacts by reducing transmission and recurrence.³⁹ Several vaccine candidates are in development, including toxoid-based formulations. The CLOVER trial evaluated a detoxified toxin A/B vaccine and demonstrated safety, although primary efficacy endpoints were not met.⁴⁰ Other candidates, such as the bivalent toxoid vaccine Cdiffense™, have been discontinued due to insufficient efficacy, underscoring ongoing challenges in this area.

2.4. Emerging vaccine platforms

2.4.1. Messenger RNA vaccines

Messenger RNA (mRNA) vaccines encode disease-specific antigens and are delivered into host cells using delivery vehicles or transfecting agents. They offer advantages in potency, safety, and rapid design, though instability and RNase susceptibility remain challenges.⁴¹ For AMR applications, mRNA vaccines targeting conserved antigens are crucial, given the rapid adaptability of ESKAPE pathogens under immune pressure.⁴²

2.4.2. Viral vector vaccines

Viral vector vaccines induce robust innate and adaptive immune responses without exposure to the complete pathogenic organism. These platforms leverage genetically modified viral genomes encoding target antigens and possess intrinsic adjuvant properties conferred by pathogen-associated molecular patterns, thereby enhancing immunogenicity.⁴³

2.4.3. Protein subunits vaccines

Protein subunit vaccines benefit from precise antigen targeting and favorable safety profiles. Gram-positive bacterial hosts have emerged as attractive expression systems, offering advantages in oral vaccine delivery, muco-adhesion, genetic tractability, and scalable industrial production.⁴⁴

2.4.4. Outer membrane vesicle-based vaccines

Gram-negative bacteria inherently secrete OMVs and contribute to environmental adaptation. OMV-

based vaccines provide increased immunogenicity, decreased reactogenicity, and enhanced safety via genetic modification. Although obstacles persist in attaining high-density surface expression of heterologous antigens, OMV platforms continue to hold promise for combating complex and drug-resistant pathogens.⁴⁵

3. Novel non-antibiotic therapeutics

The rapid global escalation of AMR has intensified the need for therapeutic strategies that extend beyond conventional antibiotic development.⁴⁶ Given the slow pace of antibiotic innovation and the accelerating emergence of multidrug-resistant pathogens, there has been a shift in focus toward non-antibiotic alternatives that can control bacterial infections without exacerbating resistance selection⁴⁷ (Table 1). These approaches often demonstrate comparable efficacy to antibiotics while minimizing selective pressure and preserving the host's microbial ecology.⁴⁸ Collectively, novel non-antibiotic therapeutics constitute a vital supplementary pillar alongside vaccination and antimicrobial stewardship in sustainable strategies for mitigating AMR (Figure 3).

3.1. Bacteriophage therapy

Bacteriophages are viruses that specifically infect and lyse bacterial cells while leaving human cells unharmed, making them attractive candidates for combating antibiotic-resistant infections.⁴⁹ Although phage therapy was first explored over a century ago, its clinical development declined following the introduction of antibiotics. The current AMR crisis, however, has renewed global interest in bacteriophages as precision antimicrobials.⁵⁰ Phages exert their antibacterial activity by injecting genetic material into susceptible bacteria, hijacking host cellular machinery for replication, and ultimately causing bacterial lysis.⁵¹ Unlike broad-spectrum antibiotics that indiscriminately affect both commensal and pathogenic bacteria⁵², bacteriophages exhibit remarkable specificity, targeting defined bacterial strains or species while preserving the host microbiota and reducing the risk of dysbiosis.⁵³ Their ability to co-evolve alongside bacterial populations further enhances their therapeutic potential against multidrug-resistant infections.⁵²

Clinical case reports and compassionate-use studies have demonstrated successful phage-mediated clearance of infections refractory to antibiotic therapy. Notably, phage therapy has been effective against methicillin-resistant *S. aureus* in chronic wound infections⁵⁴ and against *P. aeruginosa* infections in cystic fibrosis patients, where resistance to multiple antibiotic classes is common.⁵⁵ Despite these successes, several challenges remain.

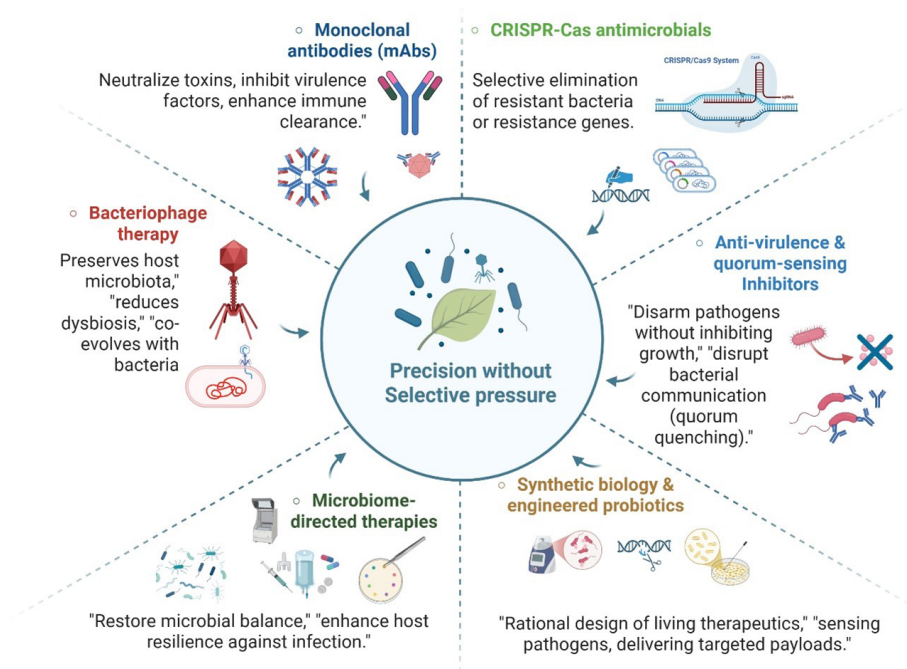


Figure 3. Spectrum of novel non-antibiotic therapeutics for the treatment of antimicrobial-resistant infections. Schematic obtained from BioRender with permission; created by Suleiman, A. (2026) <https://BioRender.com/g3ktfok>.

Abbreviation: CRISPR: Clustered regularly interspaced short palindromic repeats.

Phage therapy often requires strain-specific matching, regulatory frameworks remain insufficiently standardized, bacterial resistance to phages can arise through receptor modification or defensive systems, and host immune responses may neutralize administered phages.^{52,56,57} Nonetheless, the establishment of regional phage banks and adaptive regulatory pathways is advancing phage therapy as a viable personalized approach to addressing AMR.⁵²

3.2. Monoclonal antibodies (mAbs)

Monoclonal antibodies are emerging as powerful immunotherapeutic agents and promising alternatives for managing infections caused by drug-resistant bacteria.³⁰ mAbs exert antibacterial effects through multiple mechanisms, including neutralization of toxins, inhibition of virulence factors, opsonization, complement activation, and facilitation of phagocytic clearance.⁵⁸ These mechanisms differ fundamentally from those of small-molecule antibiotics, thereby reducing the likelihood of cross-resistance development.⁵⁹ By targeting virulence determinants rather than essential bacterial survival pathways, mAbs disarm pathogens while imposing minimal selective pressure for resistance.⁶⁰ Their high specificity limits disruption of commensal microbiota

and preserves colonization resistance.⁶¹ In addition, mAbs possess long half-lives, enabling sustained bioavailability and potentially improving treatment adherence.⁵⁸ Combination therapies pairing mAbs with antibiotics have demonstrated synergistic effects, reducing required antibiotic doses and accelerating pathogen clearance.⁶¹

Clinically, mAbs have shown efficacy against hospital-acquired pathogens, such as *S. aureus*, *P. aeruginosa*, and *A. baumannii*.⁴⁷ A human mAb targeting the DNA-binding protein II has demonstrated inhibition of biofilm formation across multiple bacterial species.⁶² Furthermore, suvratomumab, a mAb targeting *S. aureus* α -toxin, significantly reduced toxin-mediated damage in ventilator-associated pneumonia during a phase II clinical trial.⁶³ However, mAb development faces challenges, including inconsistent translation from preclinical models to clinical efficacy, high production costs limiting accessibility in low-resource settings, and immune-mediated adverse reactions such as anti-drug antibody formation.^{64–66}

3.3. CRISPR-Cas antimicrobials

CRISPR-Cas systems have emerged as precision antimicrobial tools capable of selectively eliminating resistant bacteria or resistance-conferring genes.⁶⁷ These systems rely on guide RNA-directed Cas nucleases to

introduce double-strand breaks at specific genomic or plasmid targets, resulting in bacterial death or plasmid curing.⁶⁸ Two primary strategies have been proposed: pathogen-focused approaches that target essential chromosomal genes, leading to selective bacterial killing, and gene-focused approaches that eliminate resistance plasmids, restoring antibiotic susceptibility.^{69,70} While pathogen-focused strategies are suited for defined infections, gene-focused approaches offer broader ecological benefits by reducing AMR gene abundance across microbial communities.⁷¹

Despite the tremendous benefits and advancements, CRISPR-based antimicrobials face limitations related to delivery efficiency, narrow host range of phage vectors, and limited testing in complex microbial ecosystems.^{71,72} Advances in engineered phages, conjugative plasmids, and bacterial delivery systems are rapidly addressing these challenges.⁷³

3.4. Anti-virulence and quorum-sensing inhibitors

Virulence factors enable pathogens to colonize hosts, evade immunity, acquire nutrients, and cause tissue damage. These factors may be membrane-associated, secreted, or cytosolic in nature.⁷⁴ Anti-virulence therapies target these factors directly, disarming pathogens without inhibiting growth or viability.⁷⁵ Quorum sensing (QS) is a bacterial communication system regulating density-dependent behaviors, including virulence expression, biofilm formation, and stress adaptation.⁷⁶ Disruption of QS, known as quorum quenching, can attenuate pathogenicity by interfering with signaling molecule synthesis, receptor binding, signal degradation, or downstream gene activation.⁷⁷ Because anti-virulence and QS-inhibiting agents do not threaten bacterial survival, they exert reduced selective pressure for resistance and are therefore attractive for long-term infection control.⁷⁸ However, ensuring durable efficacy across genetically diverse strains and preventing compensatory resistance mechanisms remain significant challenges.⁷⁹

3.5. Microbiome-directed therapies

Conventional antibiotics frequently disrupt microbial ecosystems, predisposing patients to recurrent infections and resistance development. Microbiome-directed therapies aim to restore microbial balance and enhance host resilience against infection.⁸⁰ These strategies include probiotics, fecal microbiota transplantation (FMT), engineered bacteria, and metabolite-based interventions.⁸¹ FMT is the most clinically validated microbiome-based therapy and involves the transfer of stool from a healthy donor to a recipient via multiple

delivery routes.⁸² It has demonstrated superior efficacy in treating recurrent *C. difficile* infections compared with antibiotic therapy.⁸¹ Probiotics have also shown benefit under certain gastrointestinal conditions, though outcomes vary depending on strain specificity and disease context.⁸³ The recent regulatory approval of microbiome-derived therapeutics marks a transition from experimental approaches to standardized clinical interventions.⁸²

3.6. Synthetic biology and engineered probiotics

Synthetic biology enables the rational design of living therapeutics capable of sensing pathogens, responding to environmental cues, and delivering targeted antimicrobial functions.⁸⁴ Engineered probiotics can be programmed to secrete bacteriocins, antimicrobial peptides, quorum-quenching enzymes, or CRISPR-Cas systems targeting resistance genes.^{85,86} These living systems can also detect pathogen-associated signals and release therapeutic payloads with high specificity, offering adaptive and self-regulating infection control strategies.^{87,88} While biosafety and containment remain important considerations, engineered probiotics represent a powerful convergence of microbiology, immunology, and synthetic biology in the fight against AMR.

4. Integrating vaccines and novel therapeutics into global antimicrobial-resistance strategies

A valuable approach to conceptualizing AMR is not as a solitary biomedical issue awaiting a singular “next antibiotic,” but as a systems failure: too much infection, too much empirical prescribing, too little prevention, and too little capacity to deploy alternatives quickly.⁴ Forecasts of AMR burden to mid-century reinforce that incrementalism will not bend the curve.^{3,4} The strategic implication is straightforward but underaddressed: AMR strategy must become a portfolio strategy, one that simultaneously expands prevention (vaccines), diversifies treatment options (novel therapeutics), and modernizes the governance layers (policy, regulation, implementation, and surveillance) that decide whether science becomes impact.^{11,29} To translate promises into impact, integration must occur across the entire pipeline, from research and development (R & D) through policy, regulation, implementation, and surveillance (Figure 4; Table 2).

4.1. Research and development priorities

The most common R & D mistake in AMR is to optimize for novelty rather than deployability. A portfolio approach reframes priorities around three deliverables: prevent more infections, treat what breaks through, and slow the evolution

Table 1. Comparison of conventional antibiotics and emerging non-antibiotic therapeutics in AMR management

Feature	Conventional antibiotics ⁹	Bacteriophage therapy ⁵²	Monoclonal antibodies ⁶¹	CRISPR-based antimicrobials ⁶⁷	Microbiome-directed therapies ⁸⁰
Mechanism of action	Broad-spectrum killing or inhibition of bacterial growth	Targeted lysis of specific bacterial strains	Neutralization of toxins or virulence factors; immune-mediated clearance	Sequence-specific targeting of bacterial DNA or resistance genes	Restoration of microbial balance and colonization resistance
Specificity	Broad (often non-specific)	Highly specific (strain-level)	Highly specific (antigen-targeted)	Gene-specific (gene-level targeting)	Moderately specific (ecosystem-level modulation)
Impact on microbiome	Disruptive (can cause dysbiosis)	Minimal disruption	Minimal disruption	Minimal to moderate (depends on delivery system)	Restorative
Resistance development	High (well-documented)	Possible, but co-evolutionary dynamics may limit persistence	Low to moderate	Low (target-specific, but delivery challenges remain)	Low
Speed of action	Rapid	Moderate (requires matching to pathogen)	Moderate	Variable (depends on delivery efficiency)	Gradual
Clinical maturity	Widely established	Emerging (limited clinical use)	Moderate (some approved, others in trials)	Early-stage (experimental)	Moderate (FMT approved; others emerging)
Cost	Generally low to moderate	Moderate to high (personalized approach)	High	Currently high	Variable (moderate to high)
Scalability	High (mass production feasible)	Limited (requires phage matching and customization)	Moderate (biologic manufacturing constraints)	Limited (delivery and regulatory barriers)	Moderate (standardization challenges remain)
Regulatory complexity	Established frameworks	Evolving and variable	Established but stringent	Emerging and complex	Evolving
Suitability in LMICs	High (widely available)	Limited (infrastructure-dependent)	Limited (cost constraints)	Currently low	Emerging potential but context-dependent
Primary role in AMR strategy	Treatment (reactive)	Precision therapy for resistant infections	Adjunct or preventive therapy	Precision elimination of resistance	Prevention and recurrence control

Note: Characteristics are synthesized from current literature on vaccines and precision therapeutics^{9,52,61,67,80}

Abbreviations: AMR: Antimicrobial resistance; FMT: Fecal microbiota transplantation; LMIC: Low- and middle-income countries.

that undermines both. First, vaccines must be treated as AMR infrastructure, not optional add-ons. Evidence consistently indicates that vaccines can reduce antibiotic consumption by preventing infections and downstream complications, with measurable impacts on prescribing.^{6,11} The practical R&D priority, therefore, is to accelerate vaccines for which AMR externalities are high and the costs of failure are catastrophic: ESKAPE pathogens and other healthcare-associated drivers.^{28,30} The early clinical evaluation of a tetravalent *K. pneumoniae* bioconjugate candidate illustrates that “hard” bacterial vaccine targets can progress when antigen selection, platform, and trial strategy align.³¹ Secondly, platform innovation should be judged by whether it shortens the path from surveillance

signal to deployable product. mRNA and viral vectors may enable faster iteration and multivalent designs, but only if formulation and distribution realities are built in from day one.^{41,43} For Gram-negative threats, OMV platforms offer a pragmatic compromise: native antigen display with tunable reactogenicity and standardized manufacturing pathways.⁴⁵ The R&D principle is “platforms that update, not products that age.”

Novel therapeutics should be pursued as precision tools that reduce reliance on broad-spectrum antibiotics. Phage therapy is a strong candidate for this role because it can target resistant infections without flattening the microbiome, yet its scalability depends on infrastructures such as phage banks, rapid matching, and adaptive manufacturing^{50,52,89}

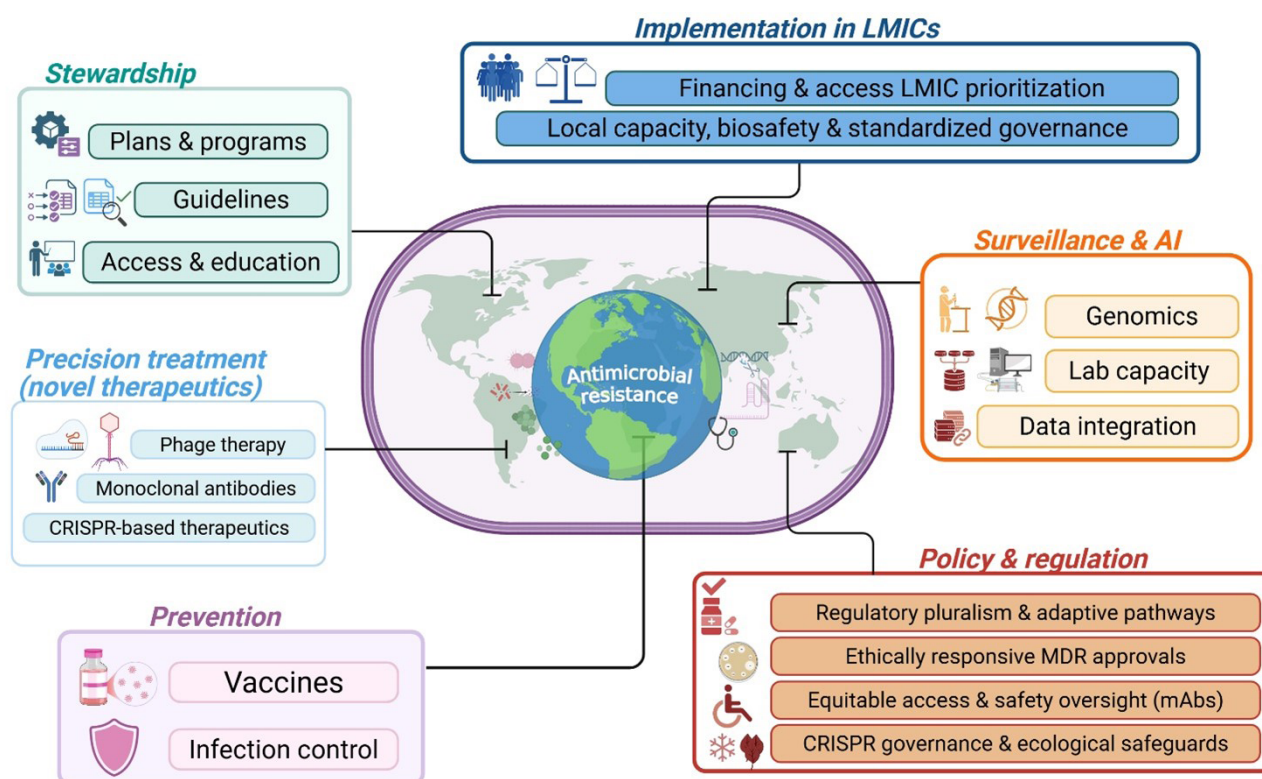


Figure 4. Integrated portfolio framework for global antimicrobial-resistance control. Schematic obtained from BioRender with permission; created by Suleiman, A. (2026) <https://BioRender.com/5uigldp>.

Abbreviation: AI: Artificial intelligence; LMICs: Low- and middle-income countries; mAbs: Monoclonal antibodies; MDR: Multidrug resistant.

mAbs are best positioned as anti-virulence or toxin neutralizers and as partners that reduce antibiotic dose intensity; their R&D pipeline should focus on endpoints that matter clinically (biofilms, severe pneumonia, and Intensive Care Unit prevention) rather than merely “binding” metrics.^{61,63} CRISPR-based antimicrobials are the ultimate precision concept, killing the resistant strain or curing the plasmid, but delivery and ecological testing in real microbial communities must be elevated from a “later” problem to a first-order design constraint.^{67,72,73}

4.2. Policy frameworks and global initiatives

The policy challenge is not the absence of AMR plans; it is that many plans still treat antibiotics as the only meaningful lever. A unique integration stance is to treat vaccines and novel therapeutics as demand-side and supply-side policies, respectively. On the demand side, vaccination is a proxy for prescribing policy. Influenza and pneumococcal vaccination reduce the clinical conditions that trigger inappropriate antibiotic use and secondary bacterial

complications, a critical point given the documented scale of inappropriate ambulatory prescribing.^{7,18} Policies that expand vaccine coverage, therefore, function as stewardship interventions with measurable outcomes in antibiotic use.^{12,14} The distinctive integration move is to embed immunization targets into AMR dashboards: coverage is not just “prevention,” it is selective-pressure management.

On the supply side, novel therapeutics require policies that reward public value rather than volume. Traditional reimbursement models that incentivize utilization; AMR solutions often require the opposite—availability with restrained use. This disparity has already compromised incentives for antibiotic innovation.² A pragmatic policy principle is “pay for readiness”: rewarding therapeutic platforms capable of being deployed against resistant outbreaks and severe cases, even if their utilization is not at a large scale. This principle is particularly pertinent to biologics and phage systems that may be employed in targeted, high-need scenarios.^{61,89} Finally, policies should

harness the potential of “cross-protection dividends.” The prospect that meningococcal OMV vaccines may reduce the risk of gonorrhea suggests that immunization strategies can confer AMR benefits beyond their primary purpose. This observation warrants consideration in future vaccine assessments and investment decisions.^{32,33}

4.3. Regulatory and ethical considerations

Most policy integration efforts often falter when regulations treat every innovation as if it were a traditional pharmaceutical pill. Therefore, this perspective piece advocates regulatory pluralism: various tools require distinct approval logics while upholding stringent safety and quality standards. Phage therapy exemplifies this issue most clearly. Its strain specificity and the requirement for cocktail updates conflict with fixed product licensing frameworks. This is not solely a technical matter; it is an ethical concern. Patients with refractory, multidrug-resistant infections frequently face time-sensitive decisions that challenge conventional evidence-gathering timelines.^{52,56} An adaptive pathway, based on standardized manufacturing quality, bank governance, and post-deployment monitoring, can ensure safety while enabling rapid learning and adjustment.

Monoclonal antibodies introduce a distinct ethical dilemma: balancing scientific feasibility against equitable access. While mAbs can be highly specific and preserve microbiome integrity, their substantial costs pose the risk of concentrating benefits within affluent systems unless intentional strategies for access are implemented.^{61,64} Ethical considerations in this context are pragmatic rather than abstract, encompassing procurement, pricing policies, and tiered manufacturing approaches. Additionally, safety ethics are imperative, given the potential for hypersensitivity reactions and the development of anti-drug antibodies, necessitating rigorous pharmacovigilance and explicit patient selection guidelines.⁶⁵ CRISPR-based antimicrobials present the most unique governance challenges, as their applications extend beyond therapy to ecological objectives, such as reducing the prevalence of resistance genes. Regulators must establish standards concerning delivery vectors, off-target effects, and community-level impacts.^{68,69,72} The fundamental ethical obligation is to ensure that the pursuit of precision does not render certain risks “invisible.”

4.4. Implementation in low- and middle-income countries

A genuinely unique integration stance is low- and middle-income country (LMIC)-first design rather than “LMIC-later distribution.” World Health Organization (WHO),

alongside key partners such as Gavi, the Vaccine Alliance, and United Nations Children’s Fund, plays a critical, multifaceted role in upholding this stance. They play a vital role in prioritizing and accelerating the development and introduction of new vaccines against diseases that disproportionately burden most vulnerable populations in LMICs.⁹⁰ They also coordinate targeted implementation of vaccination via national immunization programs. Their efforts have considerably expanded the range of available vaccines against vaccine-preventable diseases, accompanied by a substantial rise in the number of new vaccine introductions globally, including in LMICs. Out of 138 LMICs, 108 have introduced at least one new vaccine since 2010.⁹¹ However, AMR burden is often exacerbated by limited diagnostics, constrained access to second-line drugs, and high infection pressure, conditions in which prevention offers outsized returns.^{2,4} Typhoid conjugate vaccines provide an instructive case study: in settings with poor sanitation and outbreaks of resistance, vaccination can rapidly reduce the incidence of resistant disease and advance health equity.^{20,21} For TB, modeling indicates that even moderately efficacious vaccines could avert deaths from drug-resistant TB, suggesting that TB vaccine innovation is not only a treatment strategy but also a resistance strategy.^{34,35} For novel therapeutics, feasibility hinges on infrastructure choices. mAbs may be constrained by cost; phage therapy may be constrained by lab capacity, but regional phage banks linked to reference labs could be a realistic model in regions with high multidrug-resistant burdens.⁵² Microbiome therapeutics and engineered probiotics are promising, yet they demand “details-first” governance: standardized production, safety assurance, and clear clinical indications.^{80,82} Synthetic biology-based therapeutics require biosafety frameworks and local capability to avoid dependence on imported solutions.^{85,86,88}

4.5. Strengthening surveillance and monitoring systems

Within an integrated AMR framework, surveillance functions as the mechanism that aligns intervention performance with resistance outcomes. Conventional monitoring systems predominantly focus on measuring resistance prevalence; however, comprehensive integration requires additional analytical dimensions, including tracking changes in antibiotic utilization, identifying interventions that reduce the severe disease burden, and evaluating whether vaccines and novel therapeutics are altering selective pressures that drive resistance evolution. Antibiotic use is a core driver of selection pressure for resistance, and trends in prescribing can precede detectable changes in resistance, making consumption surveillance essential.^{10,18} Vaccine impact should be tracked not only

by disease incidence but also by reductions in antibiotic prescribing and in the prevalence of resistant strains, outcomes that capture AMR value directly.^{6,7} For *C. difficile*, for example, vaccine trials and modeling highlight the importance of facility-level endpoints and recurrence prevention, which should be built into monitoring frameworks.^{39,40} For novel therapeutics, surveillance must include: (i) safety (immune reactions for biologics), (ii) effectiveness (real-world outcomes), and (iii) evolutionary response (phage resistance, target mutation, community shifts).^{57,65,67} Genomic surveillance strengthens this loop by detecting emergent clones and informing vaccine/therapeutic updates, which are critical if platforms such as mRNA are used iteratively.^{4,42}

5. Future directions and innovation landscape

The future trajectory of AMR control will be determined more by the strategic orchestration of predictive intelligence, combinatorial interventions, and long-term sustainability planning than by the discovery of isolated technologies. As resistance continues to outpace conventional drug development, future solutions must be anticipatory rather than reactive, adaptive rather than static, and globally deployable rather than context-limited. Achieving this shift requires a functional perspective focused on translating innovation into operational impact, enabling proactive rather than reactive AMR control strategies (Figure 5).

5.1. Predictive tools: Artificial intelligence, immuno-informatics, and genomic surveillance

The future of antimicrobial therapy increasingly depends on integrating predictive technologies that guide prevention, diagnosis, and treatment in real time. This shift is non-negotiable given the rapid advances in genomics and data-driven analytics, which now enable unprecedented resolution in understanding pathogen evolution, the emergence of resistance, and host-microbe interactions.^{95,96} Genomic surveillance based on next-generation sequencing and metagenomic approaches has become central to modern AMR intelligence. These tools enable high-resolution characterization of resistance genes, mobile genetic elements, and clonal expansion patterns across clinical, environmental, and agricultural settings, supporting early detection of emerging threats and informed intervention planning.^{93,97,98} Beyond population-level insights, single-cell RNA sequencing has further revealed heterogeneity within bacterial populations, demonstrating how resistance can arise from rare subpopulations that evade bulk analysis.⁹²

Artificial intelligence (AI) and machine learning now function as interpretive layers over these large datasets, transforming raw genomic information into actionable predictions. AI-driven diagnostics and predictive models can integrate bacterial genetic profiles with patient-specific variables to guide personalized therapeutic decisions and optimize treatment outcomes.^{94,99,100} Such tools are particularly relevant for tailoring non-antibiotic interventions, including microbiome-directed therapies and precision biologics, where effectiveness depends on individual microbial and immunological contexts.¹⁰¹ In vaccinology, immuno-informatics has emerged as a critical accelerator of antigen discovery and vaccine design. Computational epitope mapping and reverse vaccinology approaches enable rapid identification of conserved immunogenic targets, overcoming limitations associated with antigenic variability and lengthy traditional development timelines.^{102–104} Multi-epitope vaccine constructs, designed in silico, have demonstrated the potential to elicit broader and more robust immune responses than single-antigen formulations, particularly against highly diverse or rapidly evolving pathogens.^{105–107} Computationally designed candidates targeting *S. enterica* serovar Typhi and co-infecting ESKAPE pathogens further illustrate how predictive tools can reshape vaccine development for AMR-relevant targets.^{108,109}

5.2. Opportunities for combination therapies

A defining feature of the future AMR landscape is the emergence of rational combination therapies that integrate multiple non-antibiotic modalities to enhance efficacy while constraining resistance evolution. Rather than relying on single interventions, combination strategies leverage complementary mechanisms across vaccines, bacteriophages, mAbs, CRISPR-based tools, and microbiome-directed therapies.^{110–112} Vaccines play a foundational role in such combinations by reducing infection incidence and transmission, thereby lowering overall demand for antimicrobial therapy. The WHO Action Framework on Vaccines and AMR explicitly recognizes vaccination as a synergistic component of integrated AMR strategies.¹¹³ Innovations such as reverse vaccinology, nano-adjuvants, smart bioconjugates, and nucleic acid vaccines further enhance the compatibility of vaccines with adjunctive therapies.⁵

The integration of vaccines with mAbs exemplifies a functionally complementary strategy. While vaccines confer durable, long-term protection, mAbs provide immediate immunity, bridging the window before vaccine-induced responses are fully established.¹¹⁴ This dual approach is particularly valuable during outbreaks or in high-risk populations, where rapid containment of transmission

Table 2. Operational portfolio of vaccines, novel therapeutics, and surveillance tools for AMR mitigation

Portfolio component	Primary mechanism of action	Typical use cases	Key operational requirements	Risks & limitations	Critical surveillance indicators
Vaccines (existing and next generation)	Prevent infections, reduce transmission, and lower antibiotic consumption, thereby decreasing selective pressure for resistance at the population level ^{6,7}	Routine prevention; outbreak control; targeting AMR hotspots in healthcare and community settings ^{11,30}	High coverage; cold-chain and delivery infrastructure; antigen–strain match; sustainable financing ^{6,7,11,30}	Antigenic diversity; difficulty defining efficacy endpoints for some bacterial pathogens ^{11,30}	Vaccine coverage; disease incidence; antibiotic prescribing rates; proportion of resistant infections ^{6,11,30}
Bacteriophages	Targeted lysis of specific resistant strains with minimal disruption of commensal microbiota ^{50,89}	Salvage therapy; multidrug-resistant and biofilm-associated infections; well-characterized pathogens ⁸⁹	Rapid phage–pathogen matching; phage banks; standardized manufacturing and quality control ^{50,52}	Narrow host range; regulatory uncertainty; phage resistance; immune neutralization ^{52,89}	Clinical response; emergence of phage resistance; safety and immunogenicity signals ^{50,52}
Monoclonal antibodies	Neutralization of toxins or virulence factors, enhancement of immune clearance, and reduction of antibiotic dose intensity ^{61,65}	Prevention or treatment of severe infections (e.g., ICU, pneumonia); adjunctive therapy ^{63,65}	Manufacturing capacity; cost containment; appropriate antigen selection ^{1,63,65}	High cost; variable translation from preclinical to clinical efficacy; hypersensitivity reactions ^{61,63}	Real-world effectiveness; adverse immune reactions; access and cost indicators ^{61,63,65}
CRISPR-based antimicrobials	Precise elimination of resistant strains or removal of resistance genes, enabling direct control of selection pressure ^{67,72,73}	Defined infections; resistance-gene targeting in controlled or experimental settings ^{72,73}	Efficient delivery systems (phage or plasmid); off-target risk mitigation ^{67,72,73}	Delivery constraints; ecological uncertainty; limited clinical field data ^{72,73}	Target engagement; off-target effects; microbiome and ecological impact ^{67,72,73}
Anti-virulence and quorum-sensing inhibitors	Attenuation of pathogenicity without bacterial killing, potentially reducing selection for resistance ^{74,75,78}	Adjunct therapy; suppression of biofilm formation and virulence expression ^{74,78}	Broad strain coverage; validated clinical endpoints ⁷⁵	Compensatory virulence pathways; uncertain durability across genetically diverse strains ^{74,75,78}	Clinical outcomes; changes in virulence-associated phenotypes ^{74,75,78}
Microbiome-directed therapies (FMT, LBPs, probiotics)	Restoration of colonization resistance and microbial balance, reducing recurrence and antibiotic-driven dysbiosis ^{80–82}	Recurrent <i>Clostridioides difficile</i> infection; dysbiosis-associated vulnerability ^{80–82}	Donor screening and quality control; regulatory standardization; optimized delivery routes ^{80–82}	Safety and standardization challenges; variable efficacy across indications ^{80–82}	Recurrence rates; microbiome recovery metrics; adverse events ^{80–82}
Engineered probiotics and synthetic biology approaches	In situ sensing of pathogens and delivery of targeted payloads (e.g., bacteriocins, CRISPR, quorum-quenching enzymes) ^{85,86,88}	Next-generation precision interventions with scalable deployment potential ^{85,86,88}	Robust biosafety containment; manufacturing oversight; regulatory governance ^{85,88}	Environmental release concerns; long-term safety and governance challenges ^{85,88}	Containment performance; long-term safety; clinical effectiveness ⁸⁸
Surveillance and predictive tools (genomics, AI)	Enable adaptive portfolio management by detecting emergent resistance, guiding intervention updates, and informing deployment ^{4,92,93,94}	National AMR programs; outbreak response; platform optimization and updating ^{92–94}	Genomic sequencing infrastructure; data integration and sharing; analytic capacity ^{92–94}	Data inequities; challenges in interpretation and benchmarking ^{4,92–94}	Resistance trends; antibiotic use patterns; intervention-attributable impact ^{4,92–94}

Abbreviations: AI: Artificial intelligence; AMR: Antimicrobial resistance; CRISPR: Clustered regularly interspaced short palindromic repeats; ICU: Intensive Care Unit.

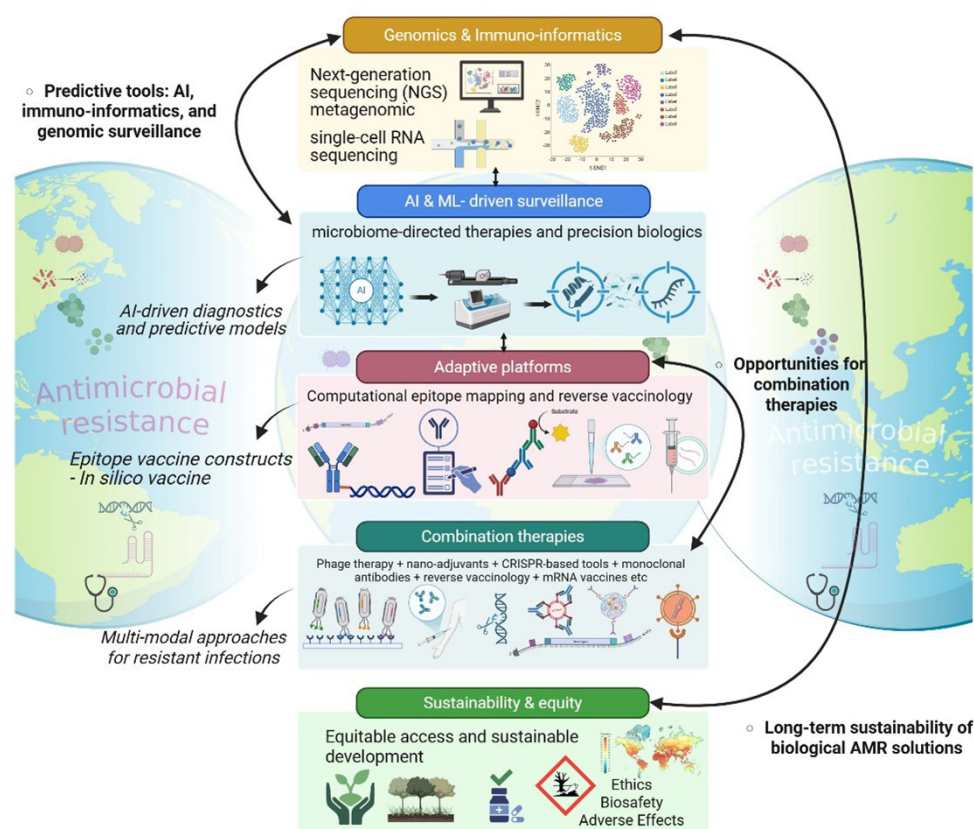


Figure 5. Future innovation landscape for combating AMR. Schematic obtained from BioRender with permission; created by Suleiman, A. (2026) <https://BioRender.com/kmgwor8>.

Abbreviations: AI: Artificial intelligence; AMR: Antimicrobial resistance; CRISPR: Clustered regularly interspaced short palindromic repeats; ML: Machine learning; NA: Nucleic acid.

is critical.^{5,115} CRISPR-based technologies have further expanded the scope of combination therapies. Advances in CRISPR-Cas12 and Cas13 systems, which target DNA and RNA, respectively, offer enhanced precision and flexibility for targeting resistance determinants.^{110,116} Experimental models demonstrate that phage-assisted CRISPR delivery can outperform either modality alone, achieving superior clearance of resistant *E. coli* in the gut and reducing systemic infection risk.^{111,117,118}

Similarly, synergistic effects have been observed when bacteriophages are combined with mAbs. In a pneumonic mouse model infected with multidrug-resistant *P. aeruginosa*, combined phage therapy and anti-PcrV antibody treatment significantly reduced lung injury and improved survival compared with monotherapy.¹¹⁹ Integration with synthetic biology further extends these possibilities, enabling engineered probiotics to deliver CRISPR-Cas systems directly within microbial communities, achieving near-complete elimination of

targeted resistant bacteria in vivo.¹²⁰

5.3. Long-term sustainability of biological antimicrobial-resistance solutions

Despite their promise, the long-term sustainability of biological AMR solutions remains a central challenge. For many novel interventions, including phage therapy, CRISPR-based antimicrobials, mAbs, and microbiome-directed therapies, long-term safety, ecological effects, and resistance dynamics are not yet fully understood.¹⁰¹ Sustainability requires longitudinal evidence; long-term prospective studies are needed to evaluate delayed adverse effects, evolutionary responses, and ecosystem-level consequences of sustained biological intervention. However, evolving regulatory frameworks and uncertainties around standardization have slowed widespread adoption.¹²¹ Phage therapy illustrates this tension clearly: its personalized, strain-specific nature raises logistical and economic challenges, particularly in regions lacking robust laboratory infrastructure. The development of extensive,

accessible phage libraries is therefore essential to support scalability and equity.^{122–124}

CRISPR technologies offer transformative precision but raise distinct ethical and biosafety concerns, including off-target effects, horizontal gene transfer, and unintended ecological disruption. Addressing these issues requires sustained investment in safety validation, governance frameworks, and ethical oversight.⁹⁴ Other biologics, such as mAbs, anti-virulence agents, and quorum-sensing inhibitors, face sustainability constraints related to cost, manufacturing complexity, immune perturbation, and delivery efficiency.^{5,115,125} Ultimately, sustainable AMR control depends on continuous innovation supported by interdisciplinary collaboration. Global frameworks must evolve to address regulatory, economic, and implementation barriers by enhancing surveillance, coordinating funding mechanisms, and fostering international cooperation.¹²⁶ Reinforcing antimicrobial stewardship across human, animal, and environmental sectors remains essential to preserving the effectiveness of both existing and emerging interventions.¹²⁷

6. Conclusion

Antimicrobial resistance has become a complex, systems-level challenge that cannot be addressed through antibiotic discovery alone.^{3,4} The evidence synthesized in this review indicates that vaccines and novel non-antibiotic therapeutics are complementary and scalable strategies that can reshape global AMR control. By preventing infections, reducing transmission, and lowering antibiotic consumption, vaccines address upstream drivers of resistance and generate population-level benefits that extend beyond individual protection.^{7,11} Advances in vaccine technologies further increase the feasibility of targeting high-priority resistant pathogens that have historically lacked effective preventive options.^{29,30} In parallel, precision-based non-antibiotic therapeutics, including bacteriophages, mAbs, CRISPR-based antimicrobials, anti-virulence agents, and microbiome-directed therapies, enable targeted management of resistant infections while minimizing disruption of host microbial ecosystems.^{61,67,89} When implemented alongside vaccination programs and antimicrobial stewardship, these approaches can reduce reliance on broad-spectrum antibiotics and help preserve the effectiveness of existing treatments.^{9,48} Collectively, these developments support a shift from a predominantly reactive, treatment-centered paradigm toward an integrated strategy emphasizing prevention, precision interventions, and adaptive implementation.^{5,29} Achieving this transition will require sustained investment in research and development, regulatory frameworks suited to biological interventions,

and implementation models that ensure equitable access across diverse healthcare settings.^{2,11} Strengthened surveillance systems and predictive tools will be essential for guiding deployment and evaluating long-term impact.^{4,10} Integrating vaccines and precision biologics into global AMR policy is therefore not optional but essential for maintaining effective infection control in the coming decades. Without such integration, resistance will continue to undermine modern medicine; with it, sustainable control of infectious diseases remains achievable.^{4,8}

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