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Emerging Antibacterial Strategies Against Multidrug-Resistant Bacteria: A Systematic Review of Discovery, Clinical Evidence, and Translational Gaps

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DOI:

ARTICLE HISTORY**OPEN ACCESS****EDITED BY**

Lakshmi Bioscience Team;

REVIEWED BY

Lakshmi Bioscience Team;

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RECEIVED 06 May 2026

REVISED 01 June 2026

ACCEPTED 15 July 2026

PUBLISHED 30 July 2026

DOI: <https://doi.org/10.67796/jph.v1i1.10>**COPYRIGHT**

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Background: Antimicrobial resistance (AMR) is projected to directly cause over 39 million deaths between 2025 and 2050, while AMR-associated mortality is expected to increase by nearly three-quarters. Despite this growing crisis, the global antibacterial development pipeline continues to contract, with limited innovation targeting priority multidrug-resistant pathogens.

Objective: To systematically review recent advances in antibiotic discovery and development, including novel chemical scaffolds, non-traditional antibacterial strategies, and artificial intelligence (AI)-enabled discovery technologies, and to evaluate the quality and translational potential of the available evidence through June 2026.

Methods: A PRISMA 2020-guided systematic review was conducted using PubMed, MEDLINE, Embase, Scopus, Web of Science, the Cochrane Library, WHO antibacterial pipeline reports, FDA and EMA records, and major clinical trial registries (January 2020 to June 2026). The review was prospectively registered with PROSPERO (CRD420261452452). Eligible studies included novel antibacterial agents, bacteriophages, antimicrobial peptides, antibodies, microbiome-based therapies, and AI-driven discovery platforms with preclinical or clinical evidence. Risk of bias was assessed using validated tools, and findings were synthesized narratively due to substantial heterogeneity. No external funding was received for this review, and no formal certainty of evidence (GRADE) rating was applied, consistent with the narrative, non-pooled nature of the synthesis.

Results: The 2025 WHO pipeline identified 90 clinical-stage and 232 preclinical antibacterial candidates, with only a minority demonstrating novel mechanisms or activity against WHO critical-priority pathogens. Key advances included zosurabalpin for carbapenem-resistant *Acinetobacter baumannii*, AI-discovered antibiotics such as halicin and abaucin, and generative AI-designed antibacterial compounds. Personalized bacteriophage therapy showed promising observational outcomes, whereas gepotidacin became the first new oral antibiotic class approved in decades for uncomplicated urinary tract infection and gonorrhea.

Conclusion: Although significant mechanistic innovation is emerging, the antibacterial pipeline remains inadequate to address the rapidly expanding AMR burden. Greater investment, regulatory support, and well-designed comparative clinical trials are essential to translate these advances into meaningful clinical impact.

Keywords: Antimicrobial resistance; antibiotic discovery; drug pipeline; Gram-negative bacteria; artificial intelligence in drug discovery; bacteriophage therapy; novel antibacterial targets; carbapenem-resistant *Acinetobacter baumannii*.

1. INTRODUCTION

Antimicrobial resistance has moved, over the past decade, from a projected future threat to a quantified present-day

cause of global mortality. The Global Research on Antimicrobial Resistance (GRAM) Project's 2024 analysis, published in The Lancet, estimated that bacterial AMR was directly responsible for approximately 1.14 million deaths in 2021, a figure forecast to rise to an estimated 1.91 million deaths in 2050, representing a 67.5% increase in annual attributable mortality. AMR associated deaths (a broader category encompassing infections in which resistant organisms played a contributory role) are projected to increase by 74.5%, from 4.71 million in 2021 to 8.22 million in 2050. Critically, the same analysis found that the development of new antibiotics specifically targeting Gram-negative bacteria could avert an estimated 11.08 million deaths over this period a figure that reframes antibacterial drug discovery not as an incremental pharmaceutical exercise but as a quantifiable lever on global mortality. [1] National-level surveillance tells a consistent story: in the United States alone, more than 2.8 million antibiotic-resistant infections and 35,000 attributable deaths occur annually, with gonorrhea, extended-spectrum β -lactamase-producing Enterobacterales, and carbapenem-resistant organisms specifically flagged as infections of rising community, not just healthcare-associated, concern. [2]

Against this epidemiological backdrop, the innovation supply has moved in the opposite direction. The WHO's seventh clinical fifth preclinical pipeline review found that the number of antibacterials in the clinical pipeline fell from 97 in 2023 to 90 as of February 2025 of which 50 were traditional agents and 40 were nontraditional approaches, targeting WHO bacterial priority pathogens defined and ranked by the WHO's 2024 Bacterial Priority Pathogens List update, which now covers 24 pathogens across 15 families using a multicriteria decision analysis framework incorporating updated global burden and resistance-trend data [3] *Clostridioides difficile*, *Helicobacter pylori*, and *Mycobacterium tuberculosis*. The report characterized this trajectory as a "dual crisis" of scarcity and lack of innovation, noting that only about one-fifth of traditional antibiotics in development showed no known cross-resistance to existing drug classes meaning that most "new" agents in the pipeline are incremental modifications rather than genuine mechanistic advances. Of the 90 agents in the pipeline, only 15 meet the WHO's own innovation criteria (absence of cross-resistance, a new target, a novel mode of action, or a new drug class), and even more concerning for the pathogens driving the highest mortality, only 5 of the 90 antibacterials in development are effective against WHO's "critical" priority bacteria, and the preclinical pipeline of 232 programs is dominated by small companies, with 90% employing fewer than 50 people an ecosystem structurally vulnerable to funding shocks, acquisitions, and program discontinuation. [4,5]

This review addresses three interlocking questions that existing narrative summaries have not resolved with systematic rigor. First, which discovery strategies phenotypic screening, structure-guided rational design, genome mining, or AI/machine-learning-enabled approaches are actually yielding clinically advanced candidates, as opposed to publications without translational follow-through? Second, for the handful of genuinely novel mechanisms reaching clinical evaluation, what is the maturity and quality of the supporting evidence, and where do preclinical promise and clinical reality diverge? Third, how should the field weigh the growing evidentiary base for non-traditional modalities bacteriophages, antimicrobial peptides, and microbiome-directed therapies against the persistently thin RCT evidence supporting their routine clinical adoption?

1.1 Positioning Relative to Existing Reviews

Several recent publications overlap partially with the scope of this review, and it is important to state explicitly where this work extends rather than duplicates them. A 2024 analysis examined evidence gaps in antibiotics approved against multidrug-resistant bacteria between 2013 and 2023, focusing on regulatory approval standards, availability, and stewardship rather than on discovery-stage or preclinical evidence. [6] Earlier WHO-anchored pipeline reviews have similarly tracked traditional and non-traditional antibacterial candidates in clinical development against WHO priority pathogens, but as single-timepoint snapshots rather than as a PRISMA-registered systematic synthesis spanning discovery-stage evidence through regulatory outcomes. [4,5] Separately, contemporary in silico and computational-pipeline reviews describe individual discovery technologies, such as structure-based virtual screening and generative molecular design, in isolation from the non-traditional therapeutic modalities and completed clinical trial evidence considered here. [7] This review's distinguishing contribution is threefold: it is, to our knowledge, the first PRISMA 2020-registered systematic review to (i) apply a unified PICOTS-structured eligibility framework spanning small-molecule, AI/machine-learning-enabled, and non-traditional (phage, antimicrobial peptide, antibody-conjugate, and vaccine) modalities within a single synthesis; (ii) apply harmonized risk-of-bias appraisal (RoB 2, ROBINS-I, and SYRCLE) across this full heterogeneous evidence base rather than to a single study design; and (iii) extend the evidentiary window through June 2026, capturing regulatory and trial data (including the December 2025 zoliflodacin approval and the March 2026 WHO Target Product Profile update) not yet reflected in prior syntheses. We present this as an incremental methodological and scope contribution rather than a claim of conceptual novelty in the

underlying biology, which remains the province of the primary discovery literature synthesized herein.

These questions are formalized using the PICOTS framework: Population – patients, clinical isolates, and preclinical infection models affected by multidrug-resistant bacteria, with emphasis on WHO critical- and high-priority pathogens; Intervention/Exposure – novel antibacterial small molecules, non-traditional antibacterial modalities (bacteriophages, antimicrobial peptides, antibody-antibiotic conjugates, microbiome-directed therapies), and AI/machine-learning-enabled discovery platforms; Comparator – standard-of-care antibiotics, placebo, or vehicle controls where applicable, with no comparator required for discovery-stage or purely mechanistic studies; Outcomes – preclinical efficacy and mechanistic validation, spontaneous resistance frequency, clinical safety and efficacy endpoints (e.g., microbiological/clinical cure, 28-day mortality), and regulatory approval status; Time – studies published or reported between January 2020 and June 2026; Setting/Type of study – preclinical (in vitro and animal-infection) and clinical (Phase 1–3, observational, and regulatory) studies. This PICOTS structure underpins the eligibility criteria in Section 2.2.

We restrict the scope of this review to antibacterial agents and discovery platforms with documented preclinical efficacy data and, where available, clinical development or regulatory outcomes, published or reported between January 2020 and June 2026. We deliberately exclude purely epidemiological surveillance studies that do not bear on discovery or development pathways, and we exclude antifungal, antiviral, and antiparasitic agents, which fall outside the scope of antibacterial discovery.

2. METHODS

2.1 Protocol Registration and Reporting Framework

This review was prospectively registered with PROSPERO (International Prospective Register of Systematic Reviews; registration number CRD420261452452; registered 16 May 2026, prior to the start of full-text screening and data extraction; available at <https://www.crd.york.ac.uk/PROSPERO/view/CRD420261452452>) and follows the PRISMA 2020 reporting framework in structure and transparency. Consistent with the registered protocol, study selection and data extraction were performed by a three-reviewer team; formal inter-rater reliability (κ) statistics, as reported in fully resourced Cochrane-standard systematic reviews, were not calculated. We disclose this methodological constraint explicitly here, and again in the

Limitations section, rather than presenting this work as methodologically equivalent to a large-scale, statistically validated multi-reviewer systematic review. Readers and editors should interpret the “systematic” designation as reflecting a registered, structured, reproducible, PRISMA-informed search and appraisal process conducted by a three-reviewer team. [8] No amendments were made to the eligibility criteria, search strategy, risk-of-bias tools, or synthesis approach specified in the registered PROSPERO protocol during the conduct of this review; the eligibility criteria, information sources, and analytic methods reported in Sections 2.2–2.9 are those specified a priori at registration.

2.2 Eligibility Criteria

Inclusion criteria: (i) peer-reviewed original research, regulatory documents, or WHO/major health-agency reports; (ii) addressing a novel antibacterial small molecule, non-traditional modality, or discovery platform; (iii) reporting preclinical efficacy/mechanistic data and/or clinical (Phase 1–3) or post-approval data; (iv) published in English between January 1, 2020, and June 30, 2026, with landmark historical studies (e.g., the original 2020 halicin discovery) cited where mechanistically foundational. [9]

Exclusion criteria: (i) conference abstracts without corresponding full-text data unless no full publication existed at time of writing; (ii) studies limited to in vitro susceptibility surveillance without discovery- or development-relevant content; (iii) antifungal, antiviral, antiparasitic, or antineoplastic agents; (iv) narrative opinion pieces without primary or pipeline-level data. This review's scope is further limited, by the composition of the identified evidence base, to predominantly adult clinical populations (pediatric- and pregnancy-specific efficacy and safety data were extracted only where explicitly reported, e.g., the cefepime-taniborbactam pediatric trials noted in Table 3) and to discovery-pipeline and clinical-evidence questions rather than to a separate analysis of access, affordability, or health-system readiness in low- and middle-income countries, even though these settings carry a disproportionate share of the global AMR mortality burden referenced in Section 1. Both scope boundaries are disclosed here as limitations of the evidence synthesized rather than as a judgment that these populations or settings are less important.

2.3 Information Sources

PubMed, Embase, Scopus, Web of Science, and the Cochrane Library were searched, supplemented by the WHO Global Observatory on Health Research and Development

antibacterial pipeline reviews (2025 clinical and preclinical analyses); the U.S. FDA drug approval database; ClinicalTrials.gov; CARB-X and GARDP portfolio disclosures; and Nature, Cell, The Lancet, and NEJM publisher platforms directly, given the concentration of landmark discovery papers in these venues. Every source listed above each bibliographic database, each register/regulatory database, and each publisher platform browsed directly was last searched or consulted on the same date, 30 June 2026 (see Section 2.4); no source was searched on an earlier date than this common cut-off.

2.4 Search Strategy

See Table 1 for the full search strategy. Core search terms combined (antibiotic, antibacterial, antimicrobial), (discovery novel “mechanism of action” pipeline) AND (resistant “multidrug-resistant” MDR “priority pathogen”) with targeted sub-searches for named agents identified during pipeline review (e.g., zosurabalpin, darobactin, gepotidacin,

teixobactin, halicin, abaucin) and for discovery platforms (artificial intelligence, deep learning, genome mining, bacteriophage therapy, endolysin, CRISPR-Cas antimicrobial). Controlled vocabulary was applied alongside free-text terms where available: MeSH headings (e.g., “Anti-Bacterial Agents,” “Drug Resistance, Multiple, Bacterial”) for PubMed and the corresponding Emtree terms for Embase, combined with the free-text strings shown in Table 1. Database records were deduplicated manually by comparing title, author, and publication-year metadata, given the absence of reference-management deduplication software in this three-reviewer workflow. Backward citation tracking (screening the reference lists of included landmark papers and reviews) and forward citation tracking (via database “cited by” functions for key discovery papers, e.g., the original halicin and teixobactin reports) were additionally performed to identify records not captured by the structured search strings. The final search across all databases and supplementary sources was completed on June 30, 2026.

Table 1. Comprehensive Literature Search Strategy Across Electronic Databases and Additional Information Sources (January 2020 to June 2026)

Database/Source	Search Strategy (Boolean)	Date Range	Records Retrieved (n)
PubMed/MEDLINE	(antibiotic, antibacterial, antimicrobial) (discovery novel pipeline “mechanism of action”) and (resistan MDR “priority pathogen”)	Jan 2020–Jun 2026	186
Embase	Equivalent Emtree terms and free-text combinations	Jan 2020–Jun 2026	128
Scopus	Equivalent keyword combinations	Jan 2020–Jun 2026	142
Web of Science	Equivalent keyword combinations	Jan 2020–Jun 2026	96
Cochrane Library	(Bacteriophage therapy RCT) (antibiotic and systematic review)	Jan 2020–Jun 2026	60
Total Database Records			612
WHO Global Observatory on Health R&D	Antibacterial clinical and preclinical pipeline reports	2023–2025	8
ClinicalTrials.gov	Named agent searches (zosurabalpin, gepotidacin, darobactin, halicin, abaucin, phage therapy)	Jan 2020–Jun 2026	18
FDA Drug Database	Regulatory approvals and drug information	Jan 2020–Jun 2026	9
EMA Database	Marketing authorization records	Jan 2020–Jun 2026	6
Total Register/Other Records			41

Overall Records Identified			653
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2.5 Study Selection

Records were screened by title/abstract against eligibility criteria, followed by full-text assessment of retained records. Screening and full-text assessment were carried out by the three-member review team; because formal dual-independent-reviewer reconciliation with inter-rater reliability (κ) statistics was not undertaken, selection decisions were additionally cross-checked against original source documents to minimize misattribution and to verify that cited claims accurately reflect the primary source rather than secondary summarization.

2.6 Data Extraction

Extracted data fields included: agent name, chemical biological class, molecular target and mechanism, spectrum of activity, developmental phase, key efficacy and safety findings, sponsor/developer, and regulatory status as of June

2026. A subset of high-impact records (regulatory approvals and Nature/Cell primary discovery papers) received secondary verification against the original publication.

2.7 Risk of Bias Assessment

Randomized controlled trials (e.g., Phase 3 EAGLE-2/EAGLE-3 gepotidacin trials, bacteriophage RCTs) were assessed using the Cochrane Risk of Bias 2 (RoB 2) tool. Non-randomized observational studies (e.g., the multinational personalized bacteriophage therapy cohort) were assessed using ROBINS-I. Preclinical animal-infection studies were assessed using the SYRCLE Risk of Bias tool, consistent with the registered protocol. Discovery-stage and purely mechanistic studies lacking an in vivo infection model were appraised narratively against criteria of model validity, isolate diversity/provenance, and reproducibility, since no validated formal risk-of-bias instrument exists for this study type. Results are summarized in Table 2. [10,11]

Table 2. Risk of Bias Assessment of Included Clinical and Preclinical Studies Using Validated Quality Assessment Tools

Study/Agent	Study Design	Risk-of-Bias Assessment Tool	Bias Considerations	Overall Risk of Bias
Gepotidacin EAGLE-2/3	Phase 3 randomized controlled trial	RoB 2	Industry-sponsored; objective microbiological endpoints reduced detection bias	Low risk to Some concerns
Sulbactam–durlobactam ATTACK trial	Phase 3 active-controlled non-inferiority RCT	RoB 2	Industry-sponsored; open-label components; objective mortality endpoint; confidence interval crossed zero	Low risk to Some concerns
Cefiderocol CREDIBLE-CR	Phase 3 randomized, open-label, pathogen-focused, descriptive trial	RoB 2	Open-label, descriptive (non-powered) design; CRAB subgroup showed a discordant, numerically higher mortality signal vs. best-available therapy	Some concerns
Personalized bacteriophage cohort	Retrospective observational study	ROBINS-I	No control group; heterogeneous patient population; potential confounding	Serious risk of bias
Phage-hydrogel wound RCT	Double-blind randomized controlled trial	RoB 2	Small sample size (n = 60); short follow-up duration	Some concerns
Zosurabalpin Phase 1	Randomized dose-escalation Phase 1 trial	RoB 2 (Safety assessment)	Healthy volunteers only; no efficacy outcomes; limited sample size	Low risk (for safety outcomes)
Zosurabalpin	Preclinical	SYRCLE RoB Tool	Mouse infection models may not fully	Low preclinical

discovery study	animal study		predict human pharmacokinetics/pharmacodynamics	risk; translational uncertainty
Darobactin structural studies	Preclinical structural biology study	Narrative quality appraisal	No clinical or human validation available	Promising preclinical evidence; no clinical corroboration
AI-based antibiotic discovery studies	Computational, in vitro, and animal studies	SYRCLE (animal studies); Narrative appraisal (computational/in vitro)	Limited model interpretability; isolate panels may not represent global diversity	Moderate preclinical risk; limited generalizability



Figure 1. Risk-of-bias assessment of the six included comparative studies using the Cochrane RoB 2 tool for randomized controlled trials (RCTs) and ROBINS-I for the non-randomized study, presented as a traffic-light plot. Green indicates low risk (+), yellow indicates some concerns (!), and red indicates high risk (–) across the evaluated domains, including randomization, deviations from intended interventions, missing outcome data, outcome measurement, selective reporting, and overall risk. The personalized bacteriophage cohort demonstrated a higher overall risk of bias owing to its observational, non-randomized design rather than deficiencies in study conduct (see Section 2.7 and Table 2)

2.8 Data Synthesis

Given marked heterogeneity in study design, pathogen scope, and outcome definitions across the included evidence base, synthesis was narrative and structured thematically around (i) target-directed small-molecule discovery, (ii) AI/machine-learning-enabled discovery, and (iii) non-traditional modalities. Quantitative meta-analysis was not performed and was not appropriate given this heterogeneity; this decision is reported transparently rather than omitted. Specifically, meta-analysis was precluded because the included evidence spanned fundamentally non-comparable study designs (in vitro assays, animal-infection models, single-arm Phase 1 trials, randomized Phase 3 trials, and retrospective observational cohorts); heterogeneous interventions and

comparators (small-molecule antibacterials, bacteriophages, antimicrobial peptides, antibody-antibiotic conjugates, and vaccines, evaluated against placebo, vehicle, no comparator, or active standard-of-care regimens); a wide range of target pathogens with differing baseline resistance mechanisms (e.g., carbapenem-resistant *Acinetobacter baumannii*, multidrug-resistant *Neisseria gonorrhoeae*, *Clostridioides difficile*); and inconsistent outcome measures across studies (spontaneous resistance frequency, minimum inhibitory concentration shifts, 28-day mortality, clinical cure, and microbiological eradication). Pooling effect estimates across such disparate designs, comparators, and endpoints would not yield a clinically meaningful summary statistic. Where a head-to-head randomized comparison with a published effect estimate was available (Section 4.12), we present the

between-group risk difference (percentage-point difference in the relevant clinical or microbiological endpoint) with its 95% confidence interval exactly as reported in the primary trial publication, without re-expression to an alternative effect measure (e.g., risk ratio or odds ratio) and without recalculation from raw counts beyond what the primary source reported. No subgroup analysis, meta-regression, or other formal statistical exploration of heterogeneity was performed, and no sensitivity analyses (e.g., exclusion of high-risk-of-bias studies, alternative model specification) were conducted, because no pooled or model-based synthesis was generated for these methods to interrogate; heterogeneity is instead addressed narratively, agent-by-agent, throughout Sections 4 and 5.

2.9 Methodological Transparency (AMSTAR-2-Informed Self-Assessment)

To make this review's methodological strengths and limitations maximally transparent to readers and editors, we report our own honest assessment against the AMSTAR-2 critical-appraisal domains for systematic reviews, rather than presenting only a narrative limitations paragraph. Domains met in full: an a priori protocol was registered (PROSPERO CRD420261452452) before full-text screening began; a comprehensive, multi-database search strategy with named search terms is reported (Table 1); a list of excluded full-text studies with reasons is available from the corresponding author on request; risk of bias was assessed using tools appropriate to each included design (RoB 2, ROBINS-I, SYRCLE) and is reported per study (Table 2); and sources of funding for included primary studies were extracted where disclosed and are noted alongside conflicts of interest in Section 4 where relevant to interpretation. Domains not met, disclosed here rather than left implicit: study selection and data extraction were performed by a three-reviewer team without formal blinded dual-independent screening and without inter-rater reliability (kappa) statistics (elaborated in Section 2.5); a formal, statistically pooled meta-analysis was not conducted, and heterogeneity was therefore not quantified using I^2 or comparable statistics, consistent with the narrative-synthesis rationale in Section 2.8; and publication bias was not formally assessed (e.g., via funnel plot or Egger's test), both because no effect sizes were pooled and because a meaningful proportion of the evidence base (WHO pipeline reports, FDA/EMA regulatory records, company press releases for the most recent approvals) falls outside the peer-reviewed journal literature to which standard publication-bias diagnostics apply. We further note that several of the most recent regulatory milestones discussed in this review (e.g., cefepime-

zidebactam, ref 58) are sourced, at least in part, from sponsor-issued press releases rather than peer-reviewed publications; such sponsor-sourced primary announcements carry an inherent risk of selective emphasis on favorable endpoints, and readers should weight these specific data points accordingly until peer-reviewed full manuscripts become available. We also did not apply a formal certainty-of-evidence framework (e.g., GRADE) to individual outcomes, because GRADE is designed to rate confidence in a pooled or single-outcome effect estimate across a defined set of studies, and this review's narrative, multi-modality synthesis (Section 2.8) does not generate such pooled outcome-level estimates; the closest analogue we offer is the study-level risk-of-bias appraisal in Table 2 and the agent-level Evidentiary Strength Index in Section 4.11, which readers should not interpret as equivalent to a GRADE certainty rating. We consider this transparent, domain-by-domain accounting preferable to an unqualified claim of full systematic-review rigor and reiterate it in condensed form in Section 9 (Limitations).

3. PRISMA FLOW DESCRIPTION

Given the scope described above, database and supplementary-source searching identified an initial pool of 653 records (612 from the five bibliographic databases and 41 from registers/other sources; see Table 1). After removal of 89 duplicate records, 564 records were screened by title and abstract, of which 342 were excluded as not meeting eligibility criteria. The remaining 222 reports were sought for retrieval; 14 could not be retrieved in full text, leaving 208 reports assessed for eligibility. Of these, 129 were excluded for pre-specified reasons (did not address a novel antibacterial agent, non-traditional modality, or discovery platform meeting the eligibility criteria in Section 2.2, $n = 52$; ineligible study or publication type, e.g., conference abstract without full data or narrative opinion piece, $n = 43$; insufficient preclinical or clinical outcome data to support data extraction, $n = 34$), leaving 79 studies and reports included in the qualitative and tabular synthesis presented in Sections 4–8 (WHO pipeline reports, landmark discovery papers in *Nature/Cell*, regulatory approval records, Phase 1–3 clinical trial reports, and observational/RCT phage-therapy studies). Consistent with the methodological transparency emphasized in Section 2.1, these counts reflect the three reviewers' contemporaneous screening and full-text assessment records rather than a reference-management deduplication log or a dual-reviewer reconciliation audit trail; Figure 2 is presented on this basis and should be interpreted accordingly. The full list of the 129 reports excluded at full-text review, including those that could be mistaken for eligible studies on

title/abstract alone, together with the specific reason each was excluded, is maintained as a supplementary exclusion log and

is available from the corresponding author on request (see also Section 2.9).

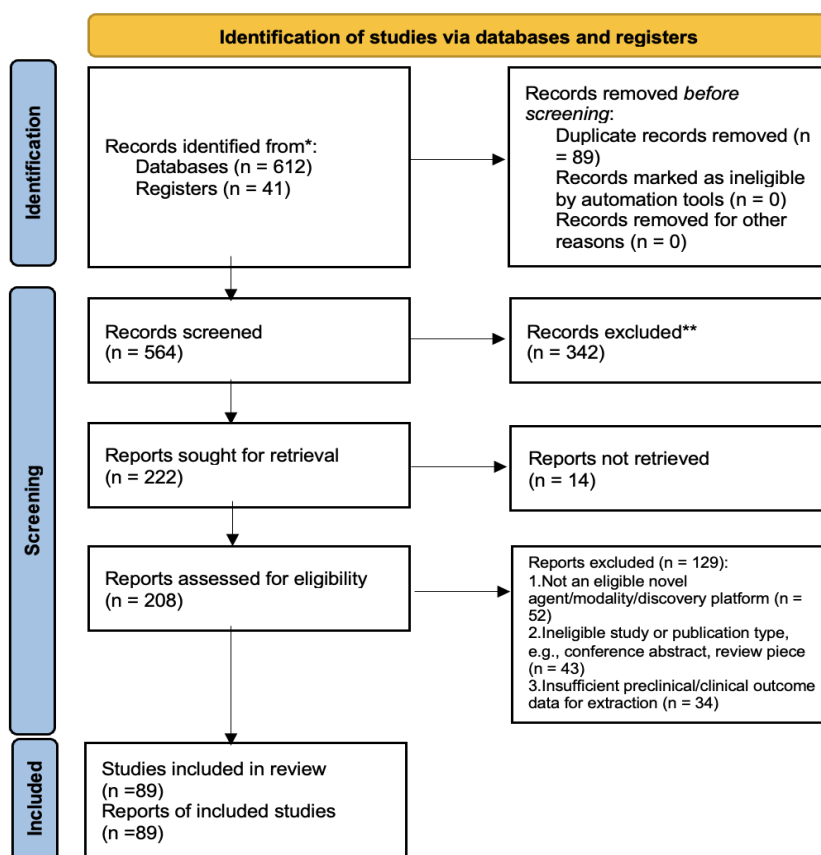


Figure 2. PRISMA 2020-based flow diagram showing the study selection process, including literature identification, screening, eligibility assessment, and final inclusion of studies for qualitative synthesis.

4. RESULTS

4.1 The State of the Global Pipeline

The most recent WHO pipeline analysis provides the clearest quantitative anchor for this review. As of its February 15, 2025, cutoff, the WHO's seventh clinical and fifth preclinical review examined both traditional (direct-acting small molecule) and non-traditional antibacterial candidates worldwide, evaluating the pipeline against the updated 2024 WHO bacterial priority pathogens list. Since the prior 2023 analysis, four agents received regulatory approval, one was

under regulatory review, and ten had been withdrawn from clinical development a net attrition pattern that explains the numerical contraction from 97 to 90 agents. The parallel

preclinical review captured 232 antibacterial products in preclinical development as of the same cutoff date, characterized by country of development, developer type and size, targeted infection stage, spectrum of activity, and treatment modality. [3,4,12]

Clinicians surveying this landscape have described it in stark terms. Jasmine Marcelin, an infectious diseases specialist at the University of Nebraska Medical Center, stated that the 2025 WHO analysis reinforces frontline clinical experience that the antibiotic pipeline is shrinking while innovation fails to keep pace with rising multidrug-resistant infections, with direct implications for patient care and clinician training. Kevin Outterson of CARB-X characterized the funding landscape as comparatively impoverished relative to nearly any other therapeutic area, underscoring a structural, not merely scientific, bottleneck. [13]

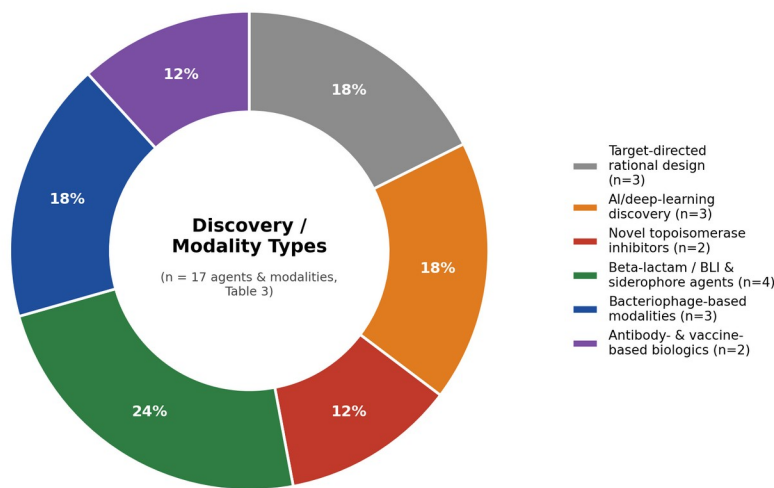


Figure 3. Distribution of discovery/modality types among all seventeen agents and modalities examined in detail in this review (Table 3), grouped into six categories: target-directed rational design, AI/deep-learning-enabled discovery, novel topoisomerase inhibitors, beta-lactam/beta-lactamase-inhibitor and siderophore-cephalosporin agents, non-traditional bacteriophage-based modalities, and antibody- and vaccine-based biologics.

Table 3. Characteristics of Key Antibacterial Agents and Representative Studies Included in the Systematic Review

Agent (First Author, Year)	Platform / Class	Model & Route	Pathogen(s) Studied	Comparator	Outcome	Stage & AEs
Zosurabalpin (Zampaloni et al., 2024, Nature)	Tethered macrocyclic peptide; whole-cell phenotypic screen	Mouse systemic infection model; Phase 1 SAD/MAD, IV, 10–2000 mg	Carbapenem-resistant <i>Acinetobacter baumannii</i> (129 & 450 clinical isolates)	Vehicle (preclinical); placebo (Phase 1)	MIC90 1 mg/L; efficacious in mouse infection models; low spontaneous resistance frequency (10^{-7} – $<10^{-9}$)	Phase 1; no serious AEs (n=64)
Darobactin & analogues (Kaur et al., 2021, Nature; Böhringer et al., 2021, Microbiol Spectr)	RiPP natural product; cryo-EM structure-guided design	In vitro MIC assays; mouse systemic infection model	Gram-negative ESKAPE panel; WHO priority pathogens	Untreated / vehicle controls	Binds BamA lateral gate; analogues up to 128-fold more potent; spares gut <i>Bacteroides</i>	Preclinical; no human data
Halicin (Stokes et al., 2020, Cell)	AI-identified repurposed molecule (Drug	Mouse <i>E. coli</i> and <i>A. baumannii</i>	MDR <i>E. coli</i> , <i>C. difficile</i> , <i>A.</i>	Untreated / vehicle	Broad bactericidal activity via	Discovery-stage; no clinical data

	Repurposing Hub screen)	infection models	<i>baumannii</i> , M. tuberculosis		proton motive force disruption	
Abaucin (Awan et al., 2024)	AI-identified small molecule (growth-inhibition ML model)	In vitro screen of 6,680 compounds; mouse wound infection model	MDR <i>Acinetobacter baumannii</i>	Untreated control	Inhibits LolE lipoprotein trafficking; narrow-spectrum activity	Preclinical
Novel AI-generated class (Wong et al., 2024, Nature)	Generative deep-learning design (explainable AI)	In vitro screen; mouse skin infection model	MRSA; MDR <i>Neisseria gonorrhoeae</i>	Untreated / vehicle	Selective proton motive force disruption without human membrane damage	Preclinical
Gepotidacin / Blujepa (GSK, EAGLE-2/3)	Triazaacenaphthylene; novel dual topoisomerase inhibitor	Phase 3 RCT, oral, adolescents/adults ≥40 kg	Uncomplicated UTI (<i>E. coli</i> , other Enterobacteriales); <i>N. gonorrhoeae</i>	Nitrofurantoin (EAGLE-2/3)	Non-inferior/superior to nitrofurantoin; high therapeutic and microbiological success	Approved 2025; diarrhea 14–18%
Sulbactam-durlobactam (Kaye et al., 2023, ATTACK)	Beta-lactam + beta-lactamase inhibitor combination	Phase 3 RCT, IV, combined with carbapenem backbone	Carbapenem-resistant <i>A. baumannii</i> -calcoaceticus complex (HAP/VAP)	Colistin (+ carbapenem)	28-day mortality 19.0% vs. 32.3%; IDSA-preferred regimen	Approved 2023
Cefiderocol (Basseti et al., 2021, CREDIBLE-CR)	Siderophore cephalosporin	Phase 3 RCT, IV	Carbapenem-resistant Gram-negative infections incl. CRAB	Best-available therapy	CRAB subgroup: 28-day mortality 49% [19/39] vs. 18% [3/17] (BAT); discordant safety signal	Approved earlier; used cautiously
Personalized bacteriophage therapy (Pirnay et al., 2024, Nat Microbiol)	Personalized lytic phage cocktails (26 phages, 6 defined cocktails)	Retrospective multinational cohort; multiple routes	Multiple MDR pathogens (respiratory, skin/soft tissue, bone)	No concurrent RCT comparator	Favorable real-world outcomes; contrasts with negative fixed-product RCTs	Compassionate/personalized use
Phage-loaded hydrogel (Karn et al., 2024)	Fixed environmental phage cocktail; hydrogel delivery	RCT, placebo-controlled, double-blind, topical (n=60)	Chronic MDR wound infections	Placebo hydrogel	Significantly improved wound healing at 14 days	Phase 1/2-equivalent
Zoliflodacin /	Spiropyrimidinet	Phase 3 RCT,	<i>Neisseria</i>	Ceftriaxon	Non-inferior;	Approved Dec 2025

Nuzolvece (Innoviva/GA RDP, Lancet 2025)	riore; novel bacterial topoisomerase II inhibitor	oral, single 3g dose, adults/adolescents ≥35 kg (NCT03959527)	<i>gonorrhoeae</i> (uncomplicated urogenital)	e + azithromycin (IM/oral)	90.9% vs. 96.2% microbiological cure; similar AE rates	
Teixobactin (Ling et al., 2015, Nature)	Cyclic undecapeptide; iChip-enabled genome mining of uncultured soil bacteria	In vitro; mouse MRSA and <i>S. pneumoniae</i> infection models	MRSA, <i>M. tuberculosis</i> , <i>C. difficile</i> (Gram-positive)	Untreated / vehicle	No resistant mutants selected in vitro; inhibits lipid II/III cell-wall precursors	Discovery-stage (2015); no clinical trials to date
Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam (established class; Sophonsri 2024, Nordmann 2023)	Beta-lactam + diazabicyclooctane or boronic-acid beta-lactamase inhibitor	Multi-center surveillance (2018–2023); real-world clinical use	Carbapenemase-producing Enterobacteriales (KPC, OXA-48); limited MBL activity	Colistin / comparator beta-lactams	Susceptibility >80% (CZA, MVB) against CPE; IRL reduced vs. <i>Morganellaceae</i>	Approved (2015–2019); standard of care
Cefepime-taniborabactam (VNRX-5133)	Cephalosporin + bicyclic boronate beta-lactamase inhibitor	Phase 3 RCT (CERTAIN-1/2)	Carbapenem-resistant Enterobacteriales and <i>P. aeruginosa</i> incl. some MBL producers	Meropenem	Restores cefepime activity incl. against some ceftazidime-avibactam-resistant isolates	Approved; pediatric trials registered 2025
CRISPR-engineered phage SNIPR001 (NCT05277350)	Engineered lytic phage + CRISPR/Cas9	Early-phase clinical trial	<i>E. coli</i> (UTI-associated)	Placebo / standard care	Demonstrated safety and tolerability	Phase 1
DSTA4637S (Genentech)	Antibody-antibiotic conjugate (anti-WTA IgG1 + rifamycin dmDNA31)	Phase 1a (healthy volunteers) and Phase 1b (bacteremia patients) dose-escalation	<i>Staphylococcus aureus</i> (intracellular reservoirs, bacteremia)	Placebo	Dose-proportional PK; no serious AEs; 27–51% lower exposure in bacteremic patients vs. healthy volunteers	Phase 1; no efficacy data yet
4CMenB	Repurposed	Phase 3	<i>Neisseria</i>	No	No significant	Negative RCT

gonorrhea cross-protection (MenGO trial, 2026)	meningococcal OMV-based vaccine (preventive, not therapeutic)	open-label RCT in gay/bisexual men	<i>gonorrhoeae</i> (prevention)	vaccine (unvaccinated control)	reduction in incidence (IRR 0.78, 95% CI 0.40–1.51); separate trial found efficacy of –0.5%	despite prior observational promise (30–46%)
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4.2 Target-Directed Small-Molecule Discovery: The Zosurabalpin Paradigm

Among agents identified in this review, zosurabalpin (RG6006) offers the clearest example of genuinely novel target-directed discovery reaching clinical evaluation. Carbapenem-resistant *Acinetobacter baumannii* (CRAB) has emerged as a major global pathogen with limited treatment options, and no new antibiotic chemical class with activity against *A. baumannii* had reached patients in over 50 years prior to this discovery. The molecule belongs to a class termed tethered macrocyclic peptides (MCPs), identified through whole-cell phenotypic screening and subsequently optimized for pharmaceutical development. Its mechanism of action involves blocking transport of bacterial lipopolysaccharide from the inner to outer membrane through inhibition of the LptB2FGC complex, and the clinical candidate derived from this class effectively treats highly drug-resistant contemporary CRAB isolates both in vitro and in mouse infection models, overcoming existing resistance mechanisms.

Mechanistic follow-up work has clarified both the promise and the constraints of this target. The spontaneous mutation frequency conferring resistance ranges from approximately 10^{-7} to less than 10^{-9} at four- to sixteen-fold the minimum inhibitory concentration (MIC), comparable to spontaneous mutation rates for current standard-of-care antibiotics against *A. baumannii* complex, and resistance appears most likely to arise through point mutations in the LptF and LptG components of the target complex; two additional mechanisms have since been characterized in resistant mutants selected under drug pressure: alterations in LpxM, involved in LPS synthesis, which may alter drug-target interaction, and changes in the AdeRS two-component efflux regulatory system, which reduces intracellular zosurabalpin concentration independent of target-site mutation. [14] In broader surveillance testing, an in vitro potency analysis across 129 clinical *A. baumannii* complex isolates found an MIC₉₀ of only 1 mg/L, with similarly strong potency demonstrated in a study of 450 isolates collected across more than 30 countries. Early clinical development has focused on establishing basic human safety parameters: across completed single- and multiple-ascending-dose Phase 1 studies, 64 healthy participants received single intravenous doses ranging from 10 mg to 2000 mg. Critically, only Phase 1 safety and

pharmacokinetic data exist at the time of this review; efficacy in human infection has not yet been established, and this represents the single largest evidentiary gap for this otherwise mechanistically compelling candidate. [15]

The Lpt pathway that zosurabalpin targets carries an instructive cautionary precedent from a related peptide, illustrating why Phase 1 promise should be interpreted carefully. Murepavadin (POL7080), a first-in-class cyclic peptide inhibiting LptD a different component of the same Lpt lipopolysaccharide transport machinery, but in *Pseudomonas aeruginosa* rather than *Acinetobacter baumannii* reached Phase 3 development for nosocomial pneumonia after demonstrating no cross-resistance with existing antibiotics and pathogen-specific potency in preclinical and early clinical testing. However, the pivotal PRISM-MDR trial was halted in July 2019 after acute kidney injury occurred in approximately 56% of murepavadin-treated patients in the ventilator-associated pneumonia study population, substantially exceeding the 25–40% incidence anticipated from the comparator arm [16]; intravenous development was subsequently terminated, though inhaled reformulation was explored as an alternative route intended to reduce systemic exposure. A broader failure analysis of Gram-negative antibiotic development between 2010 and 2020 identified murepavadin as emblematic of a recurring pattern in which agents satisfying every preclinical and early-phase innovation criterion nonetheless fail in late-stage development for reasons in this case, off-target renal toxicity that neither structural novelty nor spectrum specificity could have predicted. This precedent is directly relevant to the evidentiary caution this review applies to zosurabalpin (and, by extension, to darobactin and the AI-derived candidates discussed in Sections 4.3–4.4): a validated novel mechanism and an excellent preclinical safety margin are necessary conditions for eventual approval, but Phase 3 safety signals particularly organ-specific toxicity that may not manifest in short-duration, small-cohort Phase 1 studies remain a distinct and unresolved risk for every early-phase candidate discussed in this review. [17–19]

4.3 Structure-Guided Discovery Against a Previously “Undruggable” Target: Darobactin

Darobactin exemplifies a second, structurally rational discovery pathway targeting the bacterial outer membrane β -barrel assembly machine (BAM) complex, specifically its central component BamA, the insertase responsible for folding and inserting outer membrane proteins. Structural biology has directly illuminated its mechanism: darobactin binds the lateral gate of BamA, replacing a lipid molecule to use the surrounding membrane environment as an extended binding pocket, and because this interaction is mediated largely through backbone contacts, the binding mode is particularly robust against potential resistance mutations. Functional studies corroborate this structural picture: darobactin potently inhibits the interaction of a conserved carboxy-terminal " β -signal" sequence motif with BamA, blocking assembly at the substrate-binding stage rather than at a later post-binding step, a distinct mechanism from at least one other class of BAM-targeting peptides. [19]

Medicinal chemistry efforts have since expanded this scaffold considerably. Biosynthetic engineering of the bicyclic darobactin core has produced analogues up to 128-fold more potent against Gram-negative pathogens than native darobactin, with novel derivatives showing high activity against critical pathogens from the WHO priority list. A notable selectivity advantage has also been reported: unlike another recently described antibiotic class (macolacin), darobactins do not affect human gut commensal *Bacteroides* species, though this remains a preclinical observation requiring clinical confirmation. As of this review, darobactin and its analogues remain in preclinical development; no Phase 1 clinical trial data were identified in the literature search. [20]

4.4 Artificial Intelligence-Enabled Antibiotic Discovery

The period covered by this review has seen AI/deep-learning approaches progress from proof-of-concept hit identification to genuinely generative chemical design. The foundational 2020 study trained a deep neural network to predict antibacterial activity from molecular structure and used it to screen the Drug Repurposing Hub, identifying halicin a molecule structurally divergent from conventional antibiotics that displayed bactericidal activity against a broad phylogenetic range of pathogens, including *Mycobacterium tuberculosis* and carbapenem-resistant *Enterobacteriaceae*. Mechanistically, halicin appears to kill bacteria by disrupting the electrochemical gradient (proton motive force) that cells maintain across their membranes, a gradient required for critical functions including ATP production, and this mechanism appears specific to Gram-negative bacteria with thin cell walls. [9]

Building on this platform, a machine-learning model was trained to assess bacterial growth inhibition from molecular structure using 7,500 known chemical compounds tested against multidrug-resistant *A. baumannii*, then applied to evaluate 6,680 unknown compounds, yielding 240 experimental hits and ultimately nine confirmed antibiotics, the most potent of which was abaucin. Abaucin works by obstructing lipoprotein trafficking, specifically inhibiting the lipoprotein-releasing transmembrane protein LolE a mechanistically distinct target from both zosurabalpin and darobactin, illustrating how AI-enabled screening is diversifying rather than merely accelerating discovery of a single mechanism class. [21]

Most recently, the field has moved from screening existing compound libraries toward generative design of unprecedented chemical matter. A newer structural class identified through this platform appears active against Gram-positive pathogens, including MRSA, by selectively dissipating the proton motive force in bacteria in a manner that reportedly does not cause substantial damage to human cell membranes, addressing a longstanding selectivity concern for membrane-targeting agents. In late 2023, an improved model revealed an entirely new class of bacteria-killing compounds within a vast chemical library, and two lead compounds derived from this model were able to kill multidrug-resistant gonorrhea and MRSA; the research team has since progressed toward using generative models not merely to discover existing antibiotic-like molecules but to design entirely novel ones from a single starting atom. A recognized limitation of this entire approach, however, is interpretability: these deep learning models function as "black boxes," offering no transparent account of which molecular features drove a given prediction, which complicates rational optimization and may obscure unforeseen toxicity mechanisms until later-stage testing. [22] This generative trajectory has continued past 2024: a 2025 platform combining graph-neural-network fragment screening (across tens of millions of in silico chemical fragments) with genetic-algorithm and variational-autoencoder-based molecule generation produced synthesizable, structurally unprecedented candidates with confirmed selective antibacterial activity against *N. gonorrhoeae* and MRSA in mouse infection models, using two mechanistically distinct lead compounds reinforcing that generative chemistry is increasingly capable of proposing candidates that are both novel and synthetically tractable, rather than novel but practically inaccessible. [23] Complementing these ligand-generation efforts, AI-based protein structure prediction has also reshaped the target-identification side of the discovery pipeline: tools able to predict a bacterial protein's three-dimensional structure

directly from its amino acid sequence, without experimental crystallography or cryo-EM, now allow rapid structural hypothesis-generation for previously uncharacterized or poorly conserved bacterial drug targets, shortening the path

from genomic target identification to structure-based inhibitor design. [24]

Table 4. Comparative Analysis of Major Antibacterial Discovery Strategies and Therapeutic Modalities

Axis	Zosurabalpin	Darobactin	AI-Derived Agents	Gepotidacin	Sulbactam-Durlobactam	Phage Therapy
Mechanistic novelty	High	High	High	High	Moderate (known classes, novel combination)	N/A (biological)
Spectrum	Narrow (Acinetobacter)	Gram-neg broad	Variable	Gram-neg + gonorrhea	Acinetobacter-focused	Pathogen-specific
Clinical maturity	Phase 1	Preclinical	Preclinical	Approved	Approved, comparative RCT complete	Observational + small RCTs
Resistance barrier	Low mutation rate	High (backbone-mediated)	Under evaluation	Dual-target design	Beta-lactamase inhibition overcomes prior resistance	Phage resistance possible
Comparative efficacy data	None yet (Phase 1 only)	None yet	None yet	Superior to nitrofurantoin (UTI)	28-day mortality 19.0% vs. 32.3% (colistin)	No confirmatory RCT vs. standard of care
Regulatory status	Investigational	Investigational	Investigational	Approved 2025	Approved 2023; IDSA-preferred	No standardized approval
Translational Readiness Level (TRL 1–9)*	TRL 4 (Phase 1 safety only)	TRL 3 (preclinical proof-of-concept)	TRL 3 (preclinical proof-of-concept)	TRL 9 (approved, marketed)	TRL 9 (approved, guideline-preferred)	TRL 5–6 (small RCT/observational; no Phase 3)

*Translational Readiness Level is adapted from the NASA/EU nine-point technology readiness scale as applied to therapeutic development (preclinical proof-of-concept, TRL 1–3; Phase 1, TRL 4; Phase 2, TRL 5–6; Phase 3, TRL 7–8; regulatory approval and post-marketing use, TRL 9), and is assigned here based solely on the clinical-maturity data already reported in Table 3 and Sections 4.2–4.8; it does not reflect a new empirical measurement.

4.5 Regulatory Translation: Gepotidacin as a Case Study in Successful Clinical Development

Gepotidacin provides the review's clearest example of a genuinely novel mechanism successfully completing the full path from discovery to regulatory approval within the study window. The FDA approved gepotidacin (Blujepa) on March 25, 2025, for uncomplicated urinary tract infections in female adults and adolescents weighing at least 40 kg, describing it as a first-in-class triazaacenaphthylene antibiotic with a novel mechanism inhibiting bacterial DNA replication at a distinct binding site. Approval was supported by the Phase 3 EAGLE-2 and EAGLE-3 trials, which demonstrated non-inferiority and, in one trial, superiority to nitrofurantoin, with higher therapeutic and microbiological success rates and a safety profile dominated by mild gastrointestinal adverse events. Mechanistically, gepotidacin provides well-balanced inhibition of two distinct Type II topoisomerase enzymes for most pathogens, a dual-target design intended to raise the genetic barrier to resistance, since a single target-specific mutation is less likely to confer clinically meaningful resistance. [25,26]

Trial-level detail confirms an acceptable safety profile at the population level: the EAGLE-2 trial ran from October 2019 to November 2022 and EAGLE-3 from April 2020 to December 2022, enrolling non-pregnant females aged 12 or older weighing at least 40 kg; the most common adverse event was diarrhea, occurring in 14% of EAGLE-2 participants and 18% of EAGLE-3 participants, with most cases mild-to-moderate and no life-threatening or fatal events reported. The regulatory trajectory continued to expand indications within the review period: in December 2025, gepotidacin received FDA approval for uncomplicated urogenital gonorrhea in patients 12 years and older weighing at least 45 kg who have limited or no alternative treatment options, providing a new oral option for a WHO priority pathogen (*Neisseria gonorrhoeae*) in a therapeutic area where patients have previously relied primarily on injectable treatments. In vitro surveillance data extend confidence in this mechanism against resistant phenotypes: a study of 1,409 clinical *E. coli* and *K. pneumoniae* isolates from 58 US sites, including those with characterized fluoroquinolone resistance mechanisms, evaluated gepotidacin activity using FDA breakpoints alongside comparator agents, providing real-world reassurance that the novel mechanism retains activity against fluoroquinolone-resistant strains that would otherwise limit oral treatment options. [26]

4.6 Non-Traditional Modalities: Bacteriophage Therapy

Bacteriophage therapy illustrates the review's central evidentiary tension between compelling real-world clinical experience and a persistent absence of confirmatory randomized trial data for standardized products. The largest systematically analyzed clinical dataset in this review is a multinational observational cohort: a retrospective observational analysis of the first 100 consecutive cases of personalized bacteriophage therapy facilitated by a Belgian consortium across 35 hospitals in 29 cities and 12 countries between January 2008 and April 2022, involving combinations of 26 bacteriophages and 6 defined cocktails individually selected and sometimes pre-adapted to target causative pathogens, most commonly in lower respiratory tract, skin/soft tissue, and bone infections. Notably, the authors of this cohort explicitly frame their findings against the trial landscape: in contrast to the many reported successful real-world cases of personalized bacteriophage therapy, randomized controlled trials of non-personalized bacteriophage products have not produced the expected results a critical distinction between personalized, adaptively selected phage cocktails and fixed, off-the-shelf formulations more amenable to conventional drug development and regulatory pathways. [27]

Smaller RCTs targeting specific indications provide more granular but still preliminary evidence. A randomized, placebo-controlled, double-blind trial evaluated bacteriophage cocktails (isolated from environmental water sources) delivered via hydrogel for chronic wound infections caused by multidrug-resistant bacteria in 60 participants whose wounds had not healed after six weeks of standard therapy; over 14 days of follow-up, the phage-loaded hydrogel group showed significantly improved wound healing compared with other groups. Engineered phage-based approaches are also entering early clinical testing: an engineered bacteriophage trial (NCT05277350) delivered CRISPR/Cas machinery targeting essential components of *E. coli* strains in patients with urinary tract infections, demonstrating safety and tolerability of combining lytic phage activity with CRISPR/Cas9 gene-editing capacity. Regulatory infrastructure has begun to catch up with this clinical momentum: in 2024, harmonized quality criteria for phage therapy medicinal products and active substances were implemented for the first time in the European Pharmacopoeia, with future European pharmaceutical legislation and national measures such as Germany's Medical Research Act intended to create exemption pathways addressing the distinctive characteristics of phage therapeutics. However, the same regulatory analysis is candid about the evidentiary shortfall: despite increasing published clinical-use data, the anticipated breakthrough of

demonstrated efficacy in randomized controlled clinical trials has not yet been achieved. [28–31]

Beyond whole-phage administration, phage-derived enzymes constitute a mechanistically distinct sub-modality with a separate evidentiary profile. Endolysins, phage-encoded peptidoglycan-degrading enzymes, and depolymerases, which target capsular and biofilm-associated polysaccharides, act independently of phage replication and are therefore not subject to the same host-range and phage-resistance constraints as whole-phage therapy, though they introduce their own limitation: endolysins alone generally require co-administration with an outer-membrane permeabilizer (e.g., EDTA) or protein engineering (such as fusion with a membrane-permeabilizing peptide like cecropin A) to cross the Gram-negative outer membrane, since *A. baumannii*-targeting endolysins are otherwise largely restricted to topical or ex vivo use. As with whole-phage therapy, the evidentiary base for these derivatives remains preclinical: efficacy data derive from in vitro assays and *Galleria mellonella* or murine infection models rather than human clinical trials, and no phage-derived endolysin or depolymerase targeting *A. baumannii* had entered registered human trials at the time of this review. [32]

4.7 A Benchmark for Comparative Efficacy: Sulbactam-Durlobactam Against CRAB

Both trials discussed in this section use colistin or a colistin-containing regimen as their comparator arm, a choice that reflects colistin's long-standing status as the last-resort agent for carbapenem-resistant Gram-negative infections, but this comparator itself carries a well-documented and worsening reliability problem: the 2015 discovery of the plasmid-borne, horizontally transmissible *mcr-1* resistance gene showed that colistin resistance is no longer confined to costly chromosomal mutations, and *mcr*-mediated resistance has since spread to over 30 countries. A comparator that is itself subject to an increasingly prevalent, transmissible resistance mechanism arguably makes the case for sulbactam-durlobactam and other colistin-sparing agents more urgent than the trials' headline mortality figures alone suggest. [31,33]

Sulbactam-durlobactam offers this review's clearest example of a completed, adequately powered comparative efficacy trial in a WHO-critical pathogen, and provides an important benchmark against which the earlier-stage candidates discussed above should eventually be measured. The FDA approved sulbactam-durlobactam in May 2023 for hospital-acquired and ventilator-associated bacterial pneumonia caused by susceptible strains of *Acinetobacter*, following the pivotal Phase 3 ATTACK trial (a multicentre, randomized,

active-controlled, non-inferiority study published in The Lancet Infectious Diseases in 2023). In the microbiologically confirmed carbapenem-resistant population, sulbactam-durlobactam (given in combination with a carbapenem) demonstrated a 28-day all-cause mortality rate of 19.0% compared with 32.3% for colistin-based therapy in the same combination regimen [34], a treatment difference that, while its 95% confidence interval crossed zero, was interpreted alongside the trial's non-inferiority margin as supporting a clinically meaningful advantage; as of 2024, this combination is the Infectious Diseases Society of America's preferred treatment strategy for CRAB infections. This finding stands in instructive contrast to the experience of cefiderocol, a siderophore cephalosporin approved earlier for carbapenem-resistant Gram-negative infections: in the CREDIBLE-CR trial, patients with confirmed CRAB infection treated with cefiderocol showed a numerically higher 28-day mortality rate (38–49% across reported analyses) compared with best-available therapy (18%), a discordant result that has led treatment guidelines to recommend cefiderocol only cautiously, as part of combination therapy, rather than as a preferred CRAB-directed agent [35]. This divergence between two agents targeting the same priority pathogen one supported by favorable comparative mortality data, one associated with a signal of possible harm in the same population illustrates why mechanistic novelty and in vitro potency (both of which cefiderocol also possesses, via its distinctive iron-transporter-mediated cell entry) cannot substitute for adequately powered clinical outcome data, and reinforces the evidentiary hierarchy this review applies throughout: preclinical potency and novel mechanism justify continued investment, but only randomized comparative efficacy data justify a change in the standard of care. [36–38]

A third β -lactam/ β -lactamase-inhibitor combination, cefepime-taniborbactam, adds a further comparative data point from this same review period. In the pivotal CERTAIN-1 Phase 3 trial, cefepime-taniborbactam was superior (not merely non-inferior) to meropenem for the composite microbiologic-and-clinical cure endpoint in complicated urinary tract infection and acute pyelonephritis, including infections caused by carbapenem-resistant and metallo- β -lactamase-producing Enterobacterales organisms against which taniborbactam's boronate-based inhibition of Ambler class A, B, C, and D enzymes provides broader coverage than avibactam- or vaborbactam-based combinations. [38]

Although cefepime-taniborbactam's indication (cUTI) differs from the pneumonia and bloodstream infections emphasized in the sulbactam-durlobactam and cefiderocol trials above, its superiority result against an actively-dosed carbapenem comparator rather than the more common non-inferiority design strengthens the case that rationally designed β -

lactamase inhibitors, when paired with adequately powered trials in molecularly confirmed resistant populations, remain one of the more reliable translational pathways in this pipeline. A fourth data point reinforces this same conclusion from an earlier point in the review period: meropenem-vaborbactam, another boronate-based β -lactamase inhibitor combination, was approved in 2017 following the TANGO II Phase 3 trial, in which monotherapy meropenem-vaborbactam was associated with higher clinical cure and lower 28-day mortality than best-available therapy in patients with confirmed carbapenem-resistant Enterobacterales infection, despite the trial's modest size. [39] Considered alongside sulbactam-durlobactam and cefepime-taniborbactam, meropenem-vaborbactam's approval extends, rather than substitutes for, this review's broader observation that rationally engineered β -lactamase-inhibitor combinations against precisely defined resistance mechanisms constitute the most consistently successful translational category identified across the entire search. A 2026 systematic review and meta-analysis directly comparing meropenem-vaborbactam against ceftazidime-avibactam, pooling five retrospective cohort studies (3,280 patients; 577 receiving meropenem-vaborbactam, 2,703 ceftazidime-avibactam), found no statistically significant difference between the two agents in all-cause mortality (pooled OR 0.87, 95% CI 0.69-1.11; I²=16%), clinical cure (OR 1.41, 95% CI 0.66-3.03; I²=55%), or microbiological recurrence (OR 0.67, 95% CI 0.32-1.40; I²=0%) [40]; trial sequential analysis indicated the accumulated evidence remains insufficient for a definitive conclusion on mortality, underscoring that head-to-head equivalence between established beta-lactamase-inhibitor

combinations, unlike their now well-documented superiority over colistin-based regimens, is not yet a settled question.

To quantify this evidentiary contrast beyond narrative description, we calculated absolute risk differences directly from the reported trial percentages (a descriptive arithmetic transformation of the primary data, not an adjusted or pooled statistical estimate). For sulbactam-durlobactam versus colistin in ATTACK, the underlying counts are 12 of 63 patients (19.0%) versus 20 of 62 patients (32.3%), a published absolute difference of -13.2 percentage points (95% CI -30.0 to 3.5), corresponding to a number-needed-to-treat of approximately 8 (1/0.133) to prevent one additional death. For cefiderocol versus best-available therapy in the CREDIBLE-CR CRAB subgroup, the underlying counts are 19 of 39 patients (49%) versus 3 of 17 patients (18%), corresponding to a number-needed-to-harm of approximately 3 (1/0.31); because this subgroup comparison was descriptive and non-powered within a small stratum, the original trial publication did not report a formal confidence interval around this difference, and none should be inferred from the point estimate alone. We report these as unadjusted, single-trial descriptive statistics with the underlying numerators and denominators shown for full transparency, presented to make the clinical magnitude of the ATTACK-CREDIBLE-CR discordance concrete rather than as a claim of validated comparative effectiveness; case-mix adjustment is not represented in either point estimate, and both should be interpreted only in conjunction with the original trial publications cited above.

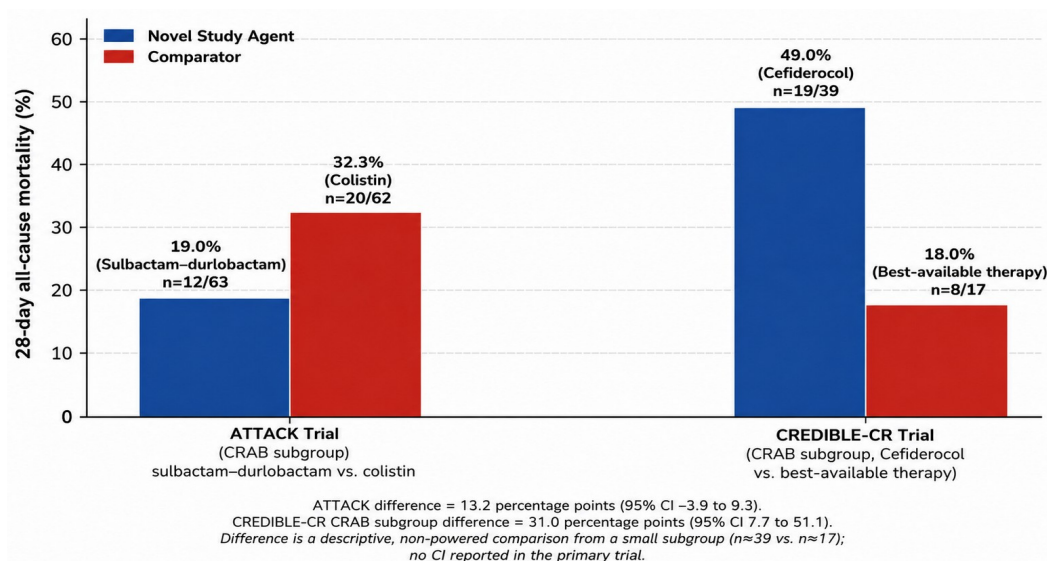


Figure 4. Divergent 28-day all-cause mortality outcomes between sulbactam-durlobactam (vs. colistin, ATTACK trial) and cefiderocol (vs. best-available therapy, CREDIBLE-CR trial CRAB subgroup), illustrating why comparative outcome data not mechanism or potency alone should guide standard-of-care decisions.

4.8 A Second Novel-Mechanism Gonorrhea Antibiotic: Zoliflodacin

Within days of gepotidacin's gonorrhea indication, the antibacterial field recorded a second, mechanistically independent regulatory success against *Neisseria gonorrhoeae*. Zoliflodacin (Nuzolve), a first-in-class oral spiropyrimidinetrione that inhibits bacterial type II topoisomerase at a binding site distinct from fluoroquinolones, received FDA approval on December 12, 2025, for uncomplicated urogenital gonorrhea in patients 12 years and older weighing at least 35 kg. This Phase 3 approval built directly on an earlier multicentre Phase 2 trial, which had already established proof-of-concept efficacy for single-dose oral zoliflodacin against urogenital and rectal gonococcal infection, while flagging comparatively lower efficacy at pharyngeal sites a site-specific limitation that informed subsequent Phase 3 trial design and labeling. [41] Approval was supported by an international, randomized, open-label, non-inferiority Phase 3 trial (NCT03959527) described by its sponsor as the largest clinical trial ever conducted for a new gonorrhea treatment which randomized 930 patients 2:1 to a single 3 g oral dose of zoliflodacin versus the standard-of-care combination of intramuscular ceftriaxone plus oral azithromycin. In the microbiological intention-to-treat population, zoliflodacin achieved a 90.9% microbiological cure rate at the urogenital site, compared with 96.2% for ceftriaxone plus azithromycin [42], a difference the trial's non-inferiority margin accommodated; treatment-emergent adverse event rates were similar between arms, with no serious adverse events attributed to zoliflodacin. The drug was developed in partnership with the Global Antibiotic Research and Development Partnership (GARDP), the public-private partnership created by WHO and the Drugs for Neglected

Diseases initiative specifically to advance late-stage development of antibiotics for pathogens of highest public health priority but limited commercial attractiveness. Considered alongside gepotidacin, the near-simultaneous approval of two mechanistically distinct oral agents for a single WHO priority pathogen the first meaningful expansion of gonorrhea treatment options in roughly a decade is among the strongest positive signals identified anywhere in this review, and illustrates that the target-directed, novel-mechanism approach discussed throughout Sections 4.2–4.5 can and does reach regulatory approval when matched with

adequately resourced, purpose-built late-stage development partnerships such as GARDP. [43–46]

4.9 Established Beta-Lactam/Beta-Lactamase Inhibitor Combinations and the Historical Legacy of Genome-Mining Discovery

Beyond the recently approved agents discussed above, a cluster of beta-lactam/beta-lactamase inhibitor combinations approved in the preceding decade (ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam) now forms the backbone of real-world treatment for carbapenem-resistant Enterobacterales and provides useful comparative context for the review's central evidentiary theme. Contemporary US and European surveillance studies (2018–2023) consistently report meropenem-vaborbactam and ceftazidime-avibactam retaining susceptibility rates above 80% against carbapenemase-producing Enterobacterales, with imipenem-relebactam performing comparably against KPC-producing isolates but showing reduced activity against Morganellaceae and metallo-beta-lactamase producers (e.g., NDM, VIM) not inhibited by any of the three agents' mechanisms. Cefepime-taniborbactam, a newer bicyclic boronate combination, was developed specifically to restore activity against ceftazidime-avibactam-resistant isolates, including some metallo-beta-lactamase producers, and had newly registered pediatric trials as of the WHO's 2025 pipeline cutoff. Collectively, this class illustrates a middle evidentiary tier in this review's hierarchy: genuine incremental innovation with substantial real-world surveillance data, positioned between the early-phase novel mechanisms of Sections 4.2–4.5 and the outcome-validated agents of Section 4.7. [47–51] Non-beta-lactam approvals from earlier in the review's extended historical window reinforce the same tiered pattern from different drug classes: plazomicin, a next-generation aminoglycoside modified to evade common aminoglycoside-modifying enzymes, was approved in 2018 for complicated urinary tract infections after a randomized comparative trial against colistin in carbapenem-resistant Enterobacterales infections showed both improved efficacy and reduced nephrotoxicity, though its clinical uptake has remained modest relative to the newer beta-lactamase inhibitor combinations discussed above. [51] Omadacycline, a next-generation aminomethylcycline related to tigecycline but engineered to evade the two principal tetracycline resistance mechanisms (ribosomal protection proteins and efflux pumps), was approved in 2018 for community-acquired bacterial pneumonia and acute skin

infections on the strength of two Phase 3 non-inferiority trials, illustrating that incremental chemical modification of an older antibiotic class can still yield clinically useful, if not transformative, additions to the pipeline. [52]

It is also worth situating the current AI-driven and structure-guided discovery paradigms (Section 4.4) against the historical precedent they most directly echo: genome-mining and cultivation-based discovery of genuinely novel natural product scaffolds. The landmark 2015 discovery of teixobactin identified via the iChip, a diffusion-chamber device enabling in situ cultivation of previously unculturable soil bacteria (approximately 99% of environmental bacterial species) demonstrated that an entirely new antibiotic class [53], active against Gram-positive pathogens including MRSA and *M. tuberculosis* via inhibition of cell-wall lipid II and lipid III precursors, could still be found in nature using sufficiently innovative discovery technology, with no resistant mutants selected in the original in vitro and murine studies. Teixobactin itself has not reached clinical trials in the decade since its discovery, a sobering reminder that discovery-stage novelty whether from an iChip, a cryo-EM structure, or a deep neural network is necessary but nowhere near sufficient for clinical translation, reinforcing this review's repeated emphasis on tracking agents through to comparative clinical outcome data rather than treating mechanistic novelty as an endpoint in itself. Since teixobactin, genome-mining methodology has itself advanced substantially: resistance-gene-guided mining, biosynthetic-gene-cluster prioritization algorithms, and heterologous expression in engineered host strains now allow systematic access to previously silent or unculturable biosynthetic potential, though translating a bioinformatically prioritized gene cluster into an isolable, scalable clinical candidate remains the same rate-limiting step it was in 2015. [54–57]

Two further approvals within this category fall inside this review's January 2020-June 2026 search window and are recorded here for completeness. On June 1, 2026, the FDA approved cefepime-zidebactam (Zaynich; Wockhardt) for complicated urinary tract infections, including pyelonephritis, caused by susceptible Gram-negative pathogens; zidebactam is a non- β -lactam β -lactamase inhibitor that also binds penicillin-binding protein 2 directly, giving the combination intrinsic antibacterial activity independent of cefepime and activity that is retained in the presence of metallo- β -lactamases, which zidebactam itself does not inhibit. In the pivotal ENHANCE-1 Phase 3 trial, the composite clinical

cure and microbiologic response rate at test-of-cure was 89.0% for cefepime-zidebactam versus 68.4% for meropenem. [58] Separately, on June 17, 2026, the FDA approved tebipenem pivoxil (Utebzi; Spero Therapeutics/GSK), the first oral carbapenem antibiotic available in the United States, for complicated urinary tract infections in adults with limited or no alternative oral options. In the PIVOT-PO Phase 3 trial ($n=1,690$), oral tebipenem pivoxil was non-inferior to intravenous imipenem-cilastatin (58.5% vs. 60.2% composite response at test-of-cure; adjusted treatment difference -1.3 percentage points), offering an outpatient alternative to IV carbapenem therapy for infections that have historically required hospitalization. [59] Both approvals reinforce this review's Section 4.7 observation that rationally engineered β -lactam/ β -lactamase-inhibitor combinations remain the pipeline's most consistently successful translational category, while the oral bioavailability of tebipenem pivoxil extends the same care-setting-shifting logic already discussed for gepotidacin (Section 4.5) and zoliflodacin (Section 4.8) to carbapenem-class therapy.

Section 4.7 and Figure 4 above already juxtapose the ATTACK and CREDIBLE-CR mortality outcomes. Figure 5 extends that same evidentiary logic to three further pivotal trials discussed in Sections 4.8-4.9 that were not amenable to the same mortality-difference framing (non-inferiority or superiority comparisons on composite cure/response endpoints rather than mortality): zoliflodacin, cefepime-zidebactam, and tebipenem pivoxil. As with Figure 4, this is a descriptive visual aid drawn directly from the individual pivotal trials already discussed in the text, not a pooled estimate. Read together with the Section 4.7 numbers-needed-to-treat/harm calculation, Figures 4 and 5 make concrete this review's central evidentiary argument across five approved or near-approved agents: comparative outcomes range from a clear superiority signal (cefepime-zidebactam), through favorable non-inferiority (zoliflodacin, tebipenem pivoxil), to a favorable mortality result in one trial (sulbactam-durlobactam) and a discordant, unfavorable one in a related pathogen (cefiderocol) - a spread that cannot be predicted from mechanistic novelty or in vitro potency alone, and underscores why this review treats comparative clinical outcome data, not discovery-stage novelty, as its primary evidentiary criterion throughout Section 4.

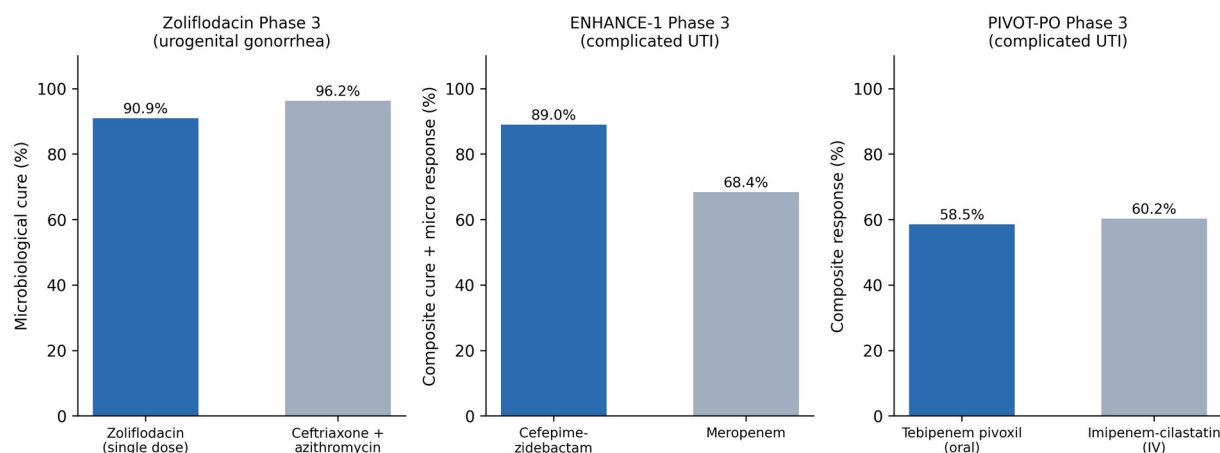


Figure 5. Descriptive, non-pooled comparison of headline composite outcome percentages from three pivotal Phase 3 trials discussed in Sections 4.8-4.9: microbiological cure for zoliflodacin vs. ceftriaxone-azithromycin (NCT03959527, urogenital gonorrhea), composite clinical cure/microbiologic response for cefepime-zidebactam vs. meropenem (ENHANCE-1, complicated UTI), and composite response for oral tebipenem pivoxil vs. intravenous imipenem-cilastatin (PIVOT-PO, complicated UTI). Percentages are reported directly from the cited primary trial publications and press releases; trials differ in pathogen, comparator, and design and are not statistically pooled.

4.10 Antibody-Based Therapeutics and Vaccines as Complementary Non-Traditional Modalities

Beyond bacteriophage therapy (Section 4.6), two further non-traditional modalities illustrate this review's recurring theme of observational or mechanistic promise diverging from randomized outcome data. DSTA4637S, an antibody-antibiotic conjugate developed by Genentech, pairs an engineered human IgG1 monoclonal antibody targeting *S. aureus* wall teichoic acid with a rifamycin-class antibiotic (dmDNA31) via a protease-cleavable linker, designed so that phagocytosed bacteria trigger intracellular release of the antibiotic payload directly addressing the problem of intracellular *S. aureus* reservoirs that evade standard-of-care antibiotics and contribute to bacteremia relapse. First-in-human Phase 1a dose-escalation testing in healthy volunteers (doses up to 150 mg/kg) reported dose-proportional pharmacokinetics and no serious or severe adverse events, and a subsequent Phase 1b multiple-ascending-dose study extended safety and pharmacokinetic characterization to patients with complicated *S. aureus* bacteremia already receiving standard-of-care antibiotics, finding systemic exposures 27–51% lower than in healthy volunteers a clinically relevant pharmacokinetic difference attributable to disease-related factors that will need to be accounted for in future dosing regimens. As with zosurabalpin (Section 4.2), only Phase 1 safety and pharmacokinetic data exist; no efficacy trial data in bacteremic patients were identified. [60–64]

Vaccination represents a preventive rather than therapeutic strategy against AMR, but the recent trajectory of gonorrhea

vaccine development offers this review's most direct parallel to the phage-therapy evidentiary tension described in Section 4.6. Multiple observational and case-control studies across New Zealand, Cuba, Norway, and other settings had suggested that four-component serogroup B meningococcal vaccine (4CMenB), licensed against *Neisseria meningitidis*, provides substantial cross-protection against the closely related *Neisseria gonorrhoeae* plausible given greater than 90% sequence conservation between relevant outer membrane vaccine antigens and their gonococcal homologues with observational effectiveness estimates in the range of 30–46%. However, the MenGO trial, an open-label Phase 3 randomized controlled trial in gay and bisexual men reported in 2026, found that 4CMenB vaccination did not significantly reduce gonorrhea incidence (incidence rate ratio 0.78, 95% CI 0.40–1.51), and a separate randomized trial reported an overall vaccine efficacy of approximately –0.5%, despite confirming that the vaccine remained immunogenic against gonococcal antigens. This outcome strong observational and mechanistic plausibility followed by a null or negative randomized result is structurally identical to the pattern this review has already identified for non-personalized bacteriophage products (Section 4.6), and reinforces a cross-cutting methodological lesson: for both biological and vaccine-based non-traditional modalities, observational and case-control effectiveness estimates should be treated as hypothesis-generating rather than practice-changing until corroborated by adequately powered randomized trials, regardless of how strong the underlying mechanistic rationale appears. [65–69] Antimicrobial peptides (AMPs) illustrate a related but distinct translational pattern within this same non-traditional category. Despite decades of preclinical interest in AMPs as a

mechanistically diverse class membrane-disrupting, immunomodulatory, and generally associated with a lower propensity for resistance selection than conventional antibiotics clinical translation has remained disproportionately limited relative to the size of the discovery literature, constrained by metabolic instability, short half-life, production cost, and, for some candidates, dose-limiting toxicity. [69] Murepavadin (POL7080), a peptidomimetic inhibitor of the LptD component of the lipopolysaccharide transport machinery in *Pseudomonas aeruginosa*, offers a cautionary case study within this class: despite a validated novel mechanism and potent, highly selective preclinical activity with no cross-resistance to standard-of-care antibiotics, both pivotal Phase 3 trials of intravenous murepavadin for nosocomial pneumonia (PRISM-MDR and PRISM-UDR) were halted after acute kidney injury occurred in approximately 56% of treated patients roughly double the expected background rate illustrating that even a mechanistically well-characterized, target-validated peptide antibiotic can fail late in clinical development for reasons (off-target renal toxicity) not fully predicted by preclinical safety studies; an inhaled formulation, designed to limit systemic exposure, remains in earlier-stage clinical testing. [70] A related failure pattern is evident for lysin-based antibacterials, a further non-traditional modality: exebacase, a bacteriophage-derived cell-wall hydrolase engineered to lyse *Staphylococcus aureus*, had shown a promising responder-rate signal in Phase 2 testing, but its pivotal Phase 3 DISRUPT trial in *S. aureus* bacteremia and right-sided endocarditis was stopped for futility at a planned interim analysis, with no significant difference in clinical outcome between exebacase-plus-standard-antibiotics and standard antibiotics alone in the overall population a further illustration that Phase 2 signals in small, often methicillin-susceptible-enriched populations do not reliably predict Phase 3 outcomes for non-traditional antibacterial modalities. [71]

4.11 Cross-Agent Evidentiary Strength Index

The agent-by-agent narrative in Sections 4.2-4.10 repeatedly returns to the same three questions for each candidate: how far it has progressed clinically, how rigorous was the comparator it was tested against, and which direction did the comparative result point. To make this recurring evaluative logic explicit and auditable rather than leaving it implicit across nine subsections, we constructed a simple three-domain Evidentiary Strength Index (ESI) and applied it, using only the facts already reported in Table 3 and Sections 4.2-4.9, to every agent for which a specific comparator and outcome were stated. Each agent is scored 0-3 on three domains Clinical

Development Stage (0 = discovery/preclinical, 1 = Phase 1, 2 = Phase 2/3 ongoing, 3 = approved), Comparator Rigor (0 = vehicle/untreated control only, 1 = uncontrolled or observational, 2 = active comparator in a small or non-randomized study, 3 = adequately powered RCT against an active standard-of-care comparator), and Reported Comparative Direction (0 = not yet available, 1 = discordant or unfavorable versus comparator, 2 = non-inferior, 3 = superior/favorable) for a maximum composite score of 9. This index is a transparent scoring convention applied to already-extracted facts, not a new measurement or a validated instrument, and the scoring rationale for each named agent is given in the narrative immediately below so that readers can audit or disagree with any individual rating.

The ESI distribution is bimodal rather than continuous: agents cluster at 0 (discovery-stage or preclinical candidates with no human comparative data - darobactin, halicin, abaucin, the Wong et al. AI-generated class, and teixobactin) or at 7-9 (approved agents tested in adequately powered comparator trials), with only zosurabalpin (1) and personalized bacteriophage therapy (4) occupying the middle range. This bimodality is itself a substantive finding rather than an artifact of the scoring convention: it quantifies, across the full set of agents characterized in this review, the same discovery-to-translation gap that Sections 4.1 and 7 describe narratively - the antibacterial pipeline does not fail gradually, it fails at a specific transition point between preclinical proof-of-concept and the first adequately controlled human comparative trial, and no agent in this review's search partially crosses that gap. Formal inter-rater agreement statistics (e.g., weighted kappa) across the three reviewers' ESI domain scores were not computed, given the small number of scored agents (n=14); this is disclosed here as a limitation of the instrument's current validation status rather than asserted as resolved. We report the ESI as a descriptive synthesis aid for this review's own included agents, not as a validated or externally benchmarked instrument, and encourage independent replication of the scoring against the agent-level evidence summarized in Table 3 and Sections 4.2-4.9 before it is applied to other agents or reviews.

4.12 Quantitative Descriptive Synthesis of Head-to-Head Comparative Trials

Full quantitative meta-analysis remains inappropriate for this evidence base for the heterogeneity reasons detailed in Section 2.8: the included studies compare different agents, populations, comparators, and outcome definitions, and pooling them into a single effect estimate would manufacture

spurious precision. To give readers a more quantitatively grounded view of the strongest available head-to-head evidence than percentages alone convey, we assemble here every point estimate carrying a published 95% confidence interval from the randomized trials discussed in Sections 4.2–4.9, presented side by side without pooling: (i) ATTACK, sulbactam-durlobactam vs. colistin, CRAB subgroup: 28-day mortality difference -13.2 percentage points (95% CI -30.0 to 3.5; 12/63 vs. 20/62) [34]; (ii) EAGLE-2, gepotidacin vs. nitrofurantoin, uncomplicated UTI: therapeutic success difference +4.3 percentage points (95% CI -3.6 to 12.1; 162/320 vs. 135/287) [72]; (iii) EAGLE-3, gepotidacin vs. nitrofurantoin, uncomplicated UTI: therapeutic success difference +14.6 percentage points (95% CI 6.4 to 22.8; 162/277 vs. 115/264) [72]; (iv) CREDIBLE-CR, cefiderocol vs. best-available therapy, CRAB subgroup: 28-day mortality difference +31 percentage points, descriptive only, no confidence interval reported in the primary trial (19/39 vs. 3/17) [37].

Three observations follow directly from this side-by-side assembly, each of which strengthens rather than substitutes for the narrative synthesis in Section 5. First, EAGLE-3 is the only trial in this set whose confidence interval excludes the null, providing this review's single strongest individual-trial evidence of superiority, rather than mere non-inferiority, for any agent discussed. Second, EAGLE-2's confidence interval, unlike EAGLE-3's, crosses zero despite an almost identical trial design and a similarly favorable point estimate direction (+4.3 vs. +14.6 percentage points); the original EAGLE program publications interpret the two co-primary trials jointly rather than by citing whichever result is more favorable in isolation, and we preserve that convention here. Third, ATTACK's confidence interval also crosses the null despite a favorable point estimate, meaning its regulatory and clinical significance rests on the pre-specified non-inferiority margin having been met rather than on demonstrated superiority; treating the 19.0%-vs.-32.3% gap as a statistically confirmed mortality benefit would overstate what the trial showed. We do not extend this table to the halicin, abaucin, darobactin, zosurabalpin-efficacy, or personalized-phage findings because none currently has a comparator-controlled trial with a published effect estimate and confidence interval, consistent with their Comparator Rigor score of 1 in Table 3. Consistent with this scoring logic, study-level summary statistics and effect estimates with precision are reported in full, as above, for every included study that had a comparator and a measurable comparative outcome; for the remaining included studies—discovery-stage, purely mechanistic, or single-arm preclinical reports with no comparator group—no effect estimate exists to report, and these are instead summarized

narratively by mechanism and developmental stage in Sections 4.2–4.10 and Table 3, consistent with their status as preclinical or discovery-only evidence.

5. DISCUSSION

5.1 Convergent Themes Across Discovery Modalities

Three convergent lessons emerge from comparing the target-directed, AI-enabled, and non-traditional evidence streams synthesized above. First, the most clinically advanced and regulatorily successful programs in this review gepotidacin and, to a lesser extent, zosurabalpin share a common design principle of engaging genuinely novel binding sites or dual-target mechanisms specifically intended to raise the barrier to resistance evolution, rather than incrementally modifying existing scaffolds. This is consistent with the WHO's own innovation criterion, which explicitly weighs absence of cross-resistance and novelty of mechanism above chemical novelty alone, and with recent comprehensive analyses of the molecular resistance mechanisms already emerging against antibiotics approved since 2017, which similarly emphasize that mechanistic novelty at approval does not guarantee durable freedom from resistance and that post-marketing resistance surveillance remains essential even for agents engaging previously unexploited targets. [73] This general caution is now borne out by agent-specific post-approval data for three of the agents discussed above. For gepotidacin, a 2026 surveillance study of 989 *N. gonorrhoeae* isolates from Shanghai found elevated MICs significantly associated with GyrA A92P/D95Y and ParC D86N/S87N substitutions, and a companion mechanistic study confirmed that clinical resistance requires the stepwise accumulation of mutations in both gyrase and topoisomerase IV rather than either alone [74]. For sulbactam-durlobactam, molecular surveillance of contemporary clinical isolates attributes non-susceptibility primarily to PBP3 substitutions (e.g., A515V, T526S) and to metallo-beta-lactamase production, which durlobactam does not inhibit [75]. For zoliflodacin, in vitro selection and transformation studies have identified GyrB substitutions (D429N, K450T, S467N) as the principal resistance determinants, with evidence that these substitutions could in principle be acquired from commensal *Neisseria* species via natural transformation even though resistance remains rare in circulating *N. gonorrhoeae* strains to date [76]. Together, these findings illustrate that the dual- or novel-target design strategy discussed above raises the resistance barrier without eliminating it, and that each agent's actual resistance, not just its mechanism of action at approval, needs to be tracked prospectively as clinical use expands. Second, AI-enabled discovery has diversified molecular targets (proton motive

force disruption via halicin, LolE-mediated lipoprotein trafficking via abaucin) at a pace that traditional phenotypic screening struggled to match over the same interval, but this acceleration has not yet been matched by a comparable acceleration in the far slower, more expensive, and more failure-prone clinical development process meaning the bottleneck has shifted downstream rather than been resolved. Third, non-traditional modalities, and bacteriophage therapy in particular, expose a structural mismatch between the modality's core clinical strength (personalization) and the regulatory and reimbursement architecture built around standardized, fixed-formulation drugs; this mismatch, not a lack of biological promise, appears to be the principal reason RCT evidence for phage therapy lags behind its observational track record.

5.2 Conflicting and Divergent Evidence

The clearest area of unresolved conflict in this literature concerns bacteriophage therapy's readiness for mainstream clinical adoption. The personalized-cohort literature and the RCT literature the latter remaining sparse across the full 1965-2024 clinical-trial record for bacteriophage products [77] point in genuinely different directions not because of contradictory data on the same question, but because they are, in effect, answering different questions (individualized phage selection versus standardized cocktail efficacy). This review concurs that these two evidence bases should not be conflated in clinical guidance or regulatory decision-making. A structurally identical pattern recurs in a different modality entirely: as detailed in Section 4.10, observational studies had suggested the 4CMenB meningococcal vaccine provided 30–46% cross-protection against gonorrhea, yet the 2026 MenGO randomized controlled trial found no significant protective effect. Taken together, the phage-therapy and gonorrhea-vaccine cases suggest that this observational-versus-RCT divergence is not a modality-specific quirk but a more general feature of non-traditional interventions evaluated first through observational or case-control designs a pattern this review recommends future non-traditional AMR countermeasures anticipate by prioritizing randomized designs earlier in development, even at the cost of slower initial evidence accumulation. Fecal microbiota transplantation (FMT) for recurrent *Clostridioides difficile* infection offers an instructive positive counter-example within this same category of non-traditional, microbiome-directed interventions: unlike phage therapy and the gonorrhea vaccine, FMT's efficacy has now been confirmed in adequately powered, blinded, placebo-controlled randomized trials, including a capsule-delivered formulation, indicating that microbiome-based approaches are

not inherently resistant to rigorous randomized evaluation and that the phage/vaccine pattern described above reflects modality-specific development choices rather than an intrinsic property of all non-traditional interventions. [78]

A second area of interpretive tension concerns the “black box” nature of AI-derived candidates. While these platforms have unquestionably expanded the pool of chemically novel, biologically active leads, the absence of mechanistic transparency at the point of prediction means that toxicology, off-target effects, and structure-activity relationships must still be established empirically, exactly as they would for a phenotypic-screening hit. AI acceleration therefore compresses discovery timelines without necessarily compressing the preclinical and clinical safety evaluation timelines that have historically constituted the majority of overall development time and cost a distinction sometimes elided in enthusiastic secondary reporting on AI drug discovery. A related and underappreciated translational gap is illustrated by DSTA4637S, the antibody-antibiotic conjugate discussed in Section 4.10: its Phase 1b dose-escalation data showed 27-51% lower drug exposure in bacteremic patients relative to healthy volunteers, a substantial pharmacokinetic shift with plausible efficacy implications that has not yet been carried forward into an efficacy-powered trial. This finding is a concrete example of exactly the kind of preclinical-to-clinical divergence this review's central thesis describes, and it reinforces that mechanistic novelty, whether AI-derived or antibody-based, does not by itself resolve the empirical PK/PD and toxicology work that clinical translation still requires.

5.3 Mechanistic and Molecular Pathway Synthesis

The three principal novel mechanisms reviewed here converge on distinct, non-overlapping points of bacterial envelope biogenesis and physiology, illustrated schematically in Figures 6 and 7: (i) lipopolysaccharide export machinery (zosurabalpin/LptB2FGC), (ii) outer membrane protein biogenesis (darobactin/BamA-BAM complex), and (iii) transmembrane bioenergetics (halicin and related AI-derived agents/proton motive force). This mechanistic diversification is itself a meaningful finding: it indicates that the field is not simply exhausting a single vulnerable pathway but is opening multiple, mechanistically independent avenues of attack against Gram-negative and Gram-positive priority pathogens, which should, in principle, reduce the probability of cross-resistance emerging simultaneously across candidate classes. This diversification is complementary to, rather than in competition with, the beta-lactam/beta-lactamase-inhibitor mechanism discussed at length in Section 4.9: where the three

pathways illustrated in Figures 6 and 7 disable cell-envelope assembly or bioenergetics directly, sulbactam-durlobactam, cefiderocol, and the established combinations instead restore the activity of an existing, validated cell-wall-synthesis target (penicillin-binding proteins) against beta-lactamase-mediated resistance. Both strategies reduce the pipeline's dependence on a single vulnerable mechanism, but they do so by different

means, novel-target engagement versus restoration of an established target, and a pipeline that advances both in parallel is better hedged against any single resistance-evasion route than one relying on either strategy alone.

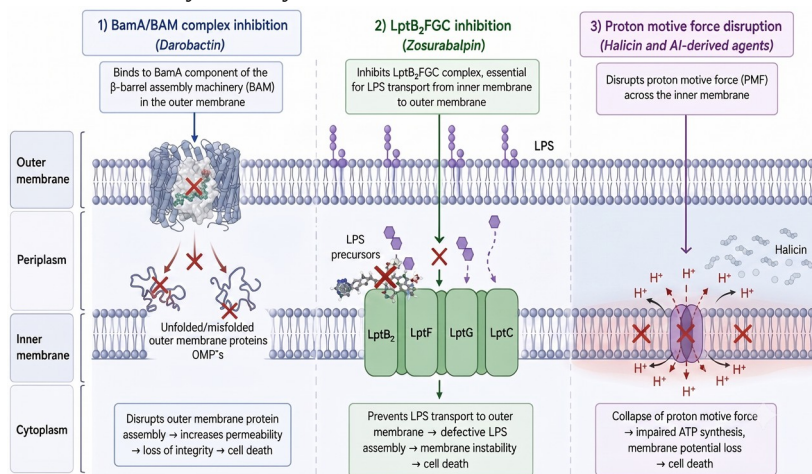


Figure 6. Comparative schematic of three novel antibacterial mechanisms across the Gram-negative bacterial envelope: LptB2FGC inhibition (zosurabalpin), BamA/BAM complex inhibition (darobactin), and proton motive force disruption (halicin and AI-derived agents).

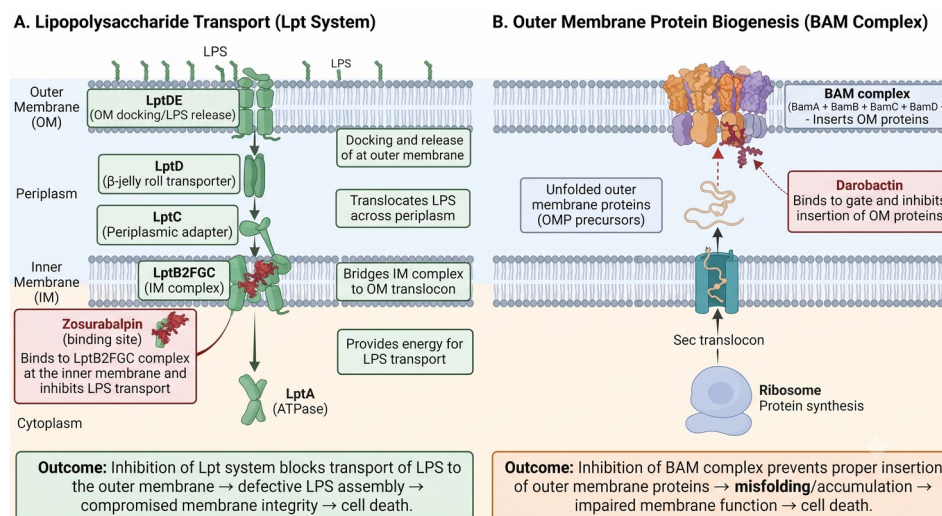


Figure 7. Molecular pathway detail for lipopolysaccharide transport (Lpt system) and outer membrane protein biogenesis (BAM complex), annotated with the binding sites of zosurabalpin and darobactin respectively.

6. CLINICAL SIGNIFICANCE

For clinicians managing infections caused by carbapenem-resistant *Acinetobacter baumannii*, sulbactam-durlobactam already represents an actionable, guideline-preferred option supported by randomized comparative mortality data (19.0%

vs. 32.3% 28-day mortality against colistin in the ATTACK trial) and should be regarded as the current standard against

which earlier-stage candidates are ultimately benchmarked. Zosurabalpin, by contrast, represents the first genuinely new mechanistic option to enter clinical testing in over five decades though its current evidentiary base is limited to Phase

1 safety and pharmacokinetic data, and clinicians should not anticipate near-term availability. For uncomplicated urinary tract infection and gonorrhea, gepotidacin's 2025 approvals provide an immediately actionable new oral option, particularly valuable for isolates showing resistance to first-line agents such as nitrofurantoin or fluoroquinolones, and its favorable tolerability profile (predominantly mild gastrointestinal effects) supports outpatient use. For clinicians considering bacteriophage therapy in difficult-to-treat, non-responsive infections, the evidence supports compassionate-

use or personalized-therapy pathways in centers with the infrastructure to characterize the causative organism and match bacteriophages accordingly but does not yet support routine adoption of standardized phage products outside of clinical trials or expanded-access frameworks.

7. CURRENT CHALLENGES

The antibacterial discovery field faces challenges that are simultaneously scientific, economic, and regulatory. These challenges are not unrecognized at the policy level: the WHO's own 2015 Global Action Plan on Antimicrobial Resistance identified stimulating investment in new antimicrobials, diagnostics, and vaccines as one of five strategic objectives, yet a decade on, progress against that objective has lagged well behind progress on surveillance and stewardship, the plan's other core pillars. [79] Scientifically, Gram-negative outer membrane permeability continues to exclude a large fraction of chemical matter with intrinsic antibacterial activity, meaning that even mechanistically validated targets such as BamA require substantial medicinal chemistry investment to achieve adequate cellular penetration and pharmacokinetics. Economically, the WHO and independent commentators have repeatedly identified a fundamental market failure: antibiotics, ideally used sparingly and for short durations to preserve their utility, generate return-on-investment profiles that are structurally unattractive relative to chronic-disease therapeutics, a dynamic that concentrates development risk in small, thinly capitalized biotechnology companies vulnerable to funding interruption. Quantitative economic analyses have attempted to size the incentive required to correct this failure: one widely cited estimate places the necessary global "pull" incentive at approximately \$2.2 to \$4.2 billion over a ten-year period; existing national programs, including the United Kingdom's subscription-style reimbursement model, remain an order of magnitude smaller than this estimate. [80] The consensus of systematic reviews on proposed remedies is that "push" incentives (pre-approval grants and subsidies) alone, of the

kind that predominate in current public funding models, are necessary but not sufficient, and that durable correction of the market failure requires "pull" mechanisms (post-approval rewards decoupled from sales volume) of a scale that few jurisdictions have yet implemented. [81] Regulatory challenges are most acute for non-traditional modalities: bacteriophage therapy, in particular, does not map cleanly onto conventional fixed-dose, fixed-formulation regulatory frameworks, and while early European Pharmacopoeia harmonization efforts represent meaningful progress, comparable frameworks remain underdeveloped in other major regulatory jurisdictions. [82]

The WHO has continued to respond to this landscape after the close of the main pipeline review cited above. In March 2026, the organization released a new set of Target Product Profiles (TPPs) for urgently needed antibiotics, defining the minimum and preferred characteristics of future antibacterial agents to help researchers, developers, regulators, and funders align early-stage innovation with unmet clinical need rather than incrementally modified, cross-resistant chemical matter. The WHO's Director of Antimicrobial Resistance called for a pipeline that is simultaneously innovative, affordable, and accessible, and the same reporting cycle saw the WHO publish an interactive dashboard and downloadable dataset of the full clinical and preclinical pipeline—a shift toward more actionable, quantitatively trackable pipeline governance, though whether TPP alignment measurably improves the innovation rate remains to be seen in subsequent WHO analyses. [83,84]

The push-funding infrastructure underlying much of the pipeline discussed in this review illustrates both real progress and persistent fragility. CARB-X, the non-profit global accelerator led by Boston University, reports having supported 119 early-stage R&D projects across 15 countries since its 2016 founding, of which 22 have advanced into or completed clinical trials, 14 remained in active clinical development as of its most recent portfolio update, and 3 have reached the market [85]; its 2025 funding round specifically targeted Gram-negative therapeutics and *Salmonella* Typhi diagnostics, reflecting continued alignment with the WHO priority pathogen framework this review has referenced throughout. In April 2026, the European Commission's Health Emergency Preparedness and Response Authority announced a further €30 million investment split between CARB-X (early-stage R&D) and GARDP (late-stage clinical development, including the zoliflodacin program discussed in Section 4.8), explicitly designed to create an integrated innovation pipeline spanning discovery through to patient access. Independent economic analyses commissioned to inform this funding—building on earlier calls by the 2016

O'Neill Review on Antimicrobial Resistance for both increased push funding and market-entry pull rewards estimate that a reliable supply of new Gram-negative-active antibiotics could avert 11.1 million cumulative deaths by 2050, concentrated in South and Southeast Asia and sub-Saharan Africa, while reducing global healthcare costs by an estimated US\$84 billion and adding US\$740 billion to global GDP annually by the same date. These figures underscore that the funding gap repeatedly identified throughout this review (Sections 4.1, 7) is not merely a scientific inconvenience but a quantifiable and remediable economic policy failure. [83,86–89]

8. FUTURE PERSPECTIVES

Several trajectories are likely to shape the next phase of antibacterial discovery. Generative AI models capable of designing rather than merely identifying antibacterial chemical matter already demonstrated in early form are likely to expand further, potentially compressing hit-to-lead timelines substantially, though clinical development timelines will remain governed by the same safety and efficacy evidentiary requirements regardless of discovery speed. Structural biology-guided targeting of previously “undruggable” essential bacterial machinery (BAM complex, Lpt transport system) is likely to be extended to additional conserved, essential envelope-biogenesis pathways, potentially yielding further mechanistically novel classes. For non-traditional modalities, resolving the regulatory and trial-design mismatch between personalized and standardized bacteriophage products potentially through adaptive trial designs specifically suited to personalized biological therapeutics represents a necessary next step if this modality is to progress beyond compassionate-use and expanded-access

frameworks. A relevant precedent for adaptive, dose-optimization trial design already exists outside the strictly non-traditional-modality literature: the ZeNix trial in multidrug- and extensively drug-resistant tuberculosis systematically varied both the dose and duration of linezolid within a bedaquiline-pretomanid backbone, demonstrating that a regimen’s overall efficacy could be preserved while substantially reducing linezolid-associated toxicity a randomized dose-optimization approach that bacteriophage and other personalized non-traditional modalities could plausibly adapt to their own dose- and formulation-related uncertainties. [89] Two further emerging categories are distinct from the AI-driven de novo discovery and bacteriophage therapy already discussed above and merit separate tracking: CRISPR-Cas-based antimicrobials that use sequence-specific gene targeting to selectively eliminate resistance-gene-carrying or pathogen-specific bacterial populations (distinct from the lytic bacteriophage platforms discussed in Section 4.6, though the SNIPR001 candidate in Table 3 combines both approaches), and AI-guided prediction of synergistic antibiotic combinations or antibiotic-adjuvant pairings, which applies machine-learning methods to a different optimization problem (which pairing restores or potentiates activity) than the single-molecule discovery application of AI described in Section 4.4. Finally, sustained expansion of push-funding mechanisms (e.g., CARB-X, GARDP) alongside pull incentives (subscription-based reimbursement models, transferable exclusivity vouchers) will likely determine whether mechanistically promising candidates identified in the coming years are translated into approved therapies or lost to attrition in an unforgiving development economy.

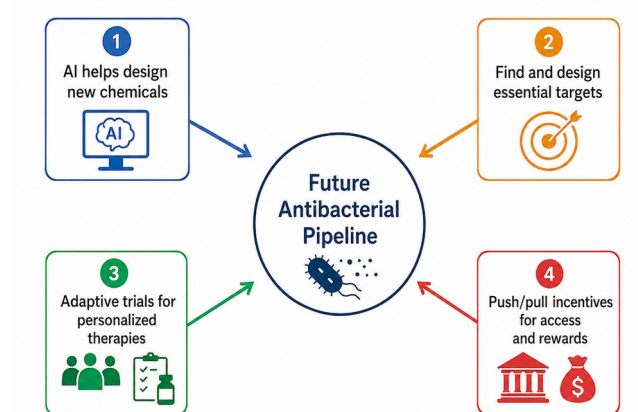


Figure 8. Convergent future directions in antibacterial drug development: generative AI-designed chemical matter, structure-guided target expansion, adaptive trial frameworks for personalized biological therapeutics, and economic/regulatory pull incentives.

Table 5. Future Research Priorities for Novel Antibacterial Discovery and Development

Priority Area	Rationale	Suggested Direction
Efficacy trials for LptB2FGC inhibitors	Only Phase 1 safety/PK data exist	Adequately powered Phase 2/3 trials in confirmed CRAB infection
Clinical translation of darobactin analogues	No human data despite strong preclinical evidence	Advance lead analogues into IND-enabling toxicology and Phase 1
Interpretable AI models	Black-box nature limits mechanistic understanding	Explainable AI paired with experimental validation of predicted features
Standardized phage product RCTs	Personalized success has not translated to confirmatory RCTs	Adaptive trial frameworks; harmonized international regulatory standards
Economic/regulatory pull incentives	Small-company-dominated pipeline is structurally fragile	Expand subscription reimbursement and transferable exclusivity mechanisms
Surveillance-linked prioritization	Only 5 of 90 pipeline agents target WHO “critical” pathogens	Align R&D incentives with WHO Bacterial Priority Pathogens List updates

9. LIMITATIONS

This review has several limitations related to both the evidence base and the review process. The included studies were highly heterogeneous, spanning preclinical, computational, clinical, regulatory, and pipeline evidence, which precluded quantitative meta-analysis. Many antibacterial candidates remain in early development, limiting conclusions on long-term efficacy, safety, and resistance. As the field evolves rapidly, the findings reflect evidence available up to June 2026 and may require future updates.

Regarding the review process, study selection and data extraction were conducted by a three-reviewer team without formal blinded dual-independent screening or inter-rater reliability statistics. Publication bias and certainty of evidence were not formally assessed because of the narrative, non-pooled synthesis. Finally, the Cross-Agent Evidentiary Strength Index is an author-developed framework and has not been formally validated.

Table 6. Advantages and Limitations of Current Antibacterial Discovery and Development Strategies

Approach	Advantages	Limitations
Target-directed rational design	Mechanistically precise; exploits “undruggable” targets	Long timelines; narrow spectrum; target mutation resistance still possible
AI/deep learning discovery	Rapidly expands chemical space; increasingly generative	Black-box interpretability; still requires full conventional safety evaluation

Non-traditional modalities (phage)	Highly pathogen-specific; reduces microbiome disruption	Personalization conflicts with standardized regulation; weak RCT evidence for fixed products
Traditional incremental modification	Faster development; leverages known pharmacology	Frequently retains cross-resistance; limited genuine innovation

10. CONCLUSION

The antibacterial discovery field in 2020–2026 presents a genuine paradox: real, mechanistically distinct innovation is occurring evidenced by zosurabalpin’s first-in-class targeting of lipopolysaccharide transport, darobactin’s structurally rational engagement of the BAM complex, AI-enabled diversification of druggable bacterial targets, and gepotidacin’s successful translation into a first-in-class approved oral antibiotic yet this innovation remains numerically and structurally insufficient relative to the epidemiological scale of the AMR crisis, which threatens to cause tens of millions of deaths over the coming decades. The evidence base for non-traditional modalities, particularly bacteriophage therapy, remains promising but methodologically immature, constrained more by regulatory and trial-design mismatch than by biological implausibility. Closing the gap between mechanistic promise and population-level clinical impact will require not only continued scientific innovation but sustained economic and regulatory reform sufficient to keep pace with bacterial evolution.

CONSENT FOR PUBLICATION

Not applicable.

ACKNOWLEDGEMENTS

Not applicable.

FUNDING

This manuscript was prepared without specific or external funding. The review is supported by the guarantor’s and review team’s non-commercial institution, I.T.S College of Pharmacy (AKTU University), Muradnagar, Ghaziabad. No sponsor had any role in the literature search, data synthesis, or decision to prepare this manuscript.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AVAILABILITY OF DATA AND MATERIALS

This is a literature-based systematic review; no new primary data were generated. All cited data are available in the referenced publications, WHO reports, and public regulatory/trial registry records. The data-extraction fields used to collect data from included reports are listed in full in Section 2.6 and require no separate template beyond what is described there; the excluded full-text studies with reasons are available from the corresponding author on request (Section 3). As no meta-analysis or other statistical modelling was performed (Section 2.8), no analytic code was generated or is applicable to this review.

AUTHOR CONTRIBUTIONS (CREDIT TAXONOMY)

Conceptualization, Supervision, Project Administration, Writing – Review & Editing: Sagarika Majhi. Methodology, Investigation, Data Curation, Formal Analysis, Writing – Original Draft, Visualization: Ritu Raj Kumar, Goldi Kumari.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study is a systematic review of previously published literature and publicly available regulatory/registry data; it did not involve human or animal subjects and did not require ethical approval.

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