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Review Article

Clinical Efficacy of Nanoparticle-Based Antibiotic Delivery Systems in Drug-Resistant Bacterial Infections: A Systematic Review

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ABSTRACT

Background: Antimicrobial resistance has substantially reduced the effectiveness of conventional antibiotics against multidrug-resistant bacterial pathogens, creating an urgent need for strategies that improve antimicrobial delivery, efficacy, and tolerability. Nanoparticle-based delivery systems have emerged as a promising approach, but recent translational evidence remains fragmented across preclinical and early clinical studies. Objective: To systematically review recent preclinical and clinical evidence on the efficacy and safety of nanoparticle-based antimicrobial delivery systems in drug-resistant bacterial infections. Methods: A systematic review with narrative synthesis was conducted in accordance with PRISMA 2020. PubMed, Scopus, Web of Science, and CENTRAL were searched for studies published from January 2019 to December 2024. Eligible studies included controlled in vivo animal studies and clinical trials evaluating antimicrobial agents encapsulated, conjugated, or otherwise delivered through nanoparticle systems against drug-resistant bacterial infections. Two reviewers independently screened studies, extracted data, and assessed risk of bias using SYRCLE for animal studies and RoB 2 for randomized trials. Owing to heterogeneity in pathogens, models, formulations, and outcomes, meta-analysis was not performed. Results: Seven studies met the final eligibility criteria, including six murine infection-model studies and one randomized clinical trial. Across the preclinical studies, nanoparticle formulations consistently improved antibacterial efficacy, with bacterial burden reductions ranging from approximately 2 to 4.5 log CFU beyond conventional comparators and survival gains of 20 to 50 percentage points in severe infection models. Liposomal vancomycin, polymeric colistin, solid lipid mupirocin, chitosan-tigecycline, silver nanoparticle-ampicillin conjugates, and liposomal linezolid all showed favorable results. The single clinical trial demonstrated that inhaled liposomal ciprofloxacin significantly prolonged time to first pulmonary exacerbation in adults with chronic Pseudomonas aeruginosa infection (hazard ratio 0.53, 95% confidence interval 0.32-0.88; p=0.01) with acceptable tolerability. Risk of bias was low in the clinical trial but frequently unclear in the preclinical literature because of incomplete reporting. Conclusion: Nanoparticle-based antimicrobial delivery systems demonstrate consistent preclinical efficacy and early clinical promise in resistant bacterial infection, particularly for liposomal platforms. However, the current evidence remains predominantly preclinical, and larger, rigorously designed clinical trials are required before routine clinical adoption can be justified. Keywords: Antimicrobial resistance; nanoparticles; liposomes; antibiotic delivery systems; multidrug-resistant bacteria; nanomedicine; systematic review

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INTRODUCTION

Antimicrobial resistance (AMR) has become one of the most consequential threats to modern medicine, undermining the effectiveness of standard antimicrobial therapy and compromising the management of common as well as life-threatening infections. Drug-resistant bacterial pathogens, particularly multidrug-resistant (MDR) and extensively drug-resistant (XDR) organisms, are associated with prolonged hospitalization, higher treatment costs, therapeutic failure, and increased mortality, placing substantial pressure on already constrained healthcare systems (1,2). Contemporary burden estimates

indicate that bacterial AMR contributed to millions of deaths globally and was directly responsible for more than one million deaths in 2019 alone, underscoring the scale and urgency of the problem (1). In parallel, the pipeline for novel antibiotics remains limited, and many currently available agents are increasingly compromised by resistance mechanisms such as enzymatic degradation, reduced membrane permeability, efflux pump overexpression, intracellular persistence, and biofilm-associated protection (2,3). These challenges have intensified interest in strategies capable of restoring or enhancing the clinical utility of existing antimicrobials rather than relying exclusively on discovery of new drug classes.

Among the most promising of these strategies is nanotechnology-enabled antimicrobial delivery. Nanoparticle-based systems have been developed to improve antibiotic pharmacokinetics, optimize tissue distribution, prolong drug retention at infected sites, and reduce premature degradation or systemic toxicity (4-6). Liposomes, polymeric nanoparticles, solid lipid nanoparticles, chitosan-based carriers, dendrimers, and metallic nanoparticles have all been investigated as platforms for antibiotic encapsulation, conjugation, or co-delivery (4,5). Their proposed therapeutic advantages are particularly relevant to resistant infections. By improving penetration into infected tissues and, in some formulations, into bacterial biofilms or intracellular compartments, these systems may overcome barriers that limit the activity of conventional free antibiotics. Sustained or targeted release can increase local drug exposure while lowering off-target toxicity, and some nanoparticle materials possess intrinsic antimicrobial or membrane-disruptive properties that may synergize with the loaded antibiotic (6-8). Collectively, these features suggest that nanoparticle-assisted delivery could enhance bacterial killing, reduce the dose required for efficacy, and potentially suppress the emergence or amplification of resistance during treatment.

A growing body of laboratory research supports these mechanistic claims, and recent in vivo studies have reported improved bacterial clearance, enhanced survival, and attenuation of inflammatory injury with nano-formulated antibiotics against clinically relevant resistant organisms such as methicillin-resistant Staphylococcus aureus (MRSA), MDR Pseudomonas aeruginosa, Acinetobacter baumannii, and vancomycin-resistant enterococci (VRE) (7-9). At the same time, early clinical investigations, particularly of liposomal anti-infective formulations, have begun to demonstrate that nanoparticle-mediated delivery may translate into more favorable efficacy or safety outcomes in selected patient populations (10). Nevertheless, the translational evidence remains fragmented. Preclinical studies vary widely in animal model, pathogen, infection site, nanocarrier architecture, route of administration, dosing strategy, and outcome measurement, which limits direct comparability across studies. Clinical evidence remains sparse, and most published human data relate to specific formulations or narrow therapeutic contexts rather than broad validation across resistant bacterial infections. As a result, although the field is often described as promising, it is still unclear which nanoparticle approaches demonstrate the most consistent therapeutic value and how far preclinical success has progressed toward clinically meaningful application.

Previous literature has largely emphasized mechanistic, formulation-focused, or in vitro perspectives on nano-antibiotic systems (4,6,8,9). While these contributions are important, they do not adequately resolve the question most relevant to translational infectious-disease research: whether nanoparticle-based antibiotic delivery improves efficacy and safety outcomes when tested in whole-animal infection models and in human subjects receiving anti-infective therapy. A focused systematic review of these higher-order data is therefore needed to distinguish theoretical promise from demonstrated therapeutic performance. This need is especially timely because the last several years have seen rapid expansion in nano-enabled drug delivery research, improvements in carrier engineering, and increasing pressure to develop clinically deployable strategies against resistant pathogens. A contemporary synthesis restricted to recent evidence is better positioned to reflect the current maturity of the field than older broad reviews that combine outdated formulations, in vitro studies, and heterogeneous anti-infective applications.

Accordingly, this systematic review was undertaken to synthesize recent preclinical and clinical evidence on nanoparticle-based antibiotic or anti-infective delivery systems evaluated against drug-resistant bacterial infections or clinically relevant anti-infective outcomes linked to resistant bacterial disease. The review was structured around the following question: in animal models or human subjects with drug-resistant bacterial infection, does nanoparticle-mediated delivery of an antimicrobial agent, compared with free drug administration, placebo, or standard formulation, improve microbiological efficacy, survival or clinical outcomes, and safety? The objective was to critically appraise the therapeutic performance, safety profile, and translational relevance of these formulations using a systematic and PRISMA 2020-aligned approach, thereby identifying the most promising directions for future clinical development and evidence generation (11).

MATERIAL AND METHODS

This review was conducted as a systematic review with narrative synthesis and was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement (11). The review question was framed using Population, Intervention, Comparator, and Outcome principles. The population comprised mammalian in vivo infection models and human participants with documented or clinically relevant drug-resistant bacterial infection. The intervention of interest was any nanoparticle-based delivery system in which an antimicrobial agent was encapsulated, conjugated, adsorbed, or otherwise associated with a nanocarrier with the purpose of improving antimicrobial delivery or therapeutic effect. Eligible comparators included the corresponding free antimicrobial drug, placebo, vehicle control, no treatment, or conventional non-nanoparticle formulations. Outcomes of interest included microbiological efficacy such as bacterial burden reduction or eradication, host-centered efficacy such as survival or clinical improvement, and safety outcomes including organ toxicity, local tolerability, and treatment-related adverse events.

A comprehensive electronic literature search was conducted in PubMed, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials to identify relevant studies published from January 1, 2019, to December 31, 2024. The search timeframe was selected to capture contemporary evidence reflecting recent advances in nanocarrier engineering and translational antimicrobial delivery. Search terms combined controlled vocabulary and free-text keywords related to resistant bacterial infection, nanotechnology-based drug delivery, and antimicrobial efficacy. The PubMed strategy was structured around three concept blocks joined with the Boolean operator AND: (“drug-resistant bacteria” OR “multidrug-resistant” OR MDR OR MRSA OR “methicillin-resistant Staphylococcus aureus” OR “Pseudomonas aeruginosa” OR “Acinetobacter baumannii” OR VRE OR “vancomycin-resistant enterococci”), AND (“nanoparticle” OR “nanocarrier” OR liposome OR “polymeric nanoparticle” OR “solid lipid nanoparticle” OR chitosan OR dendrimer OR “metal nanoparticle” OR “nano-antibiotic” OR nanomedicine), AND (“antibacterial efficacy” OR “bacterial clearance” OR “treatment outcome” OR survival OR toxicity OR safety). Search syntax was adapted for each database according to platform-specific indexing and field requirements. In addition to database searching, the reference lists of all included articles and relevant review papers were manually screened to identify additional eligible studies.

Studies were eligible if they were original peer-reviewed investigations reporting controlled in vivo preclinical experiments or clinical trials evaluating a nanoparticle-based antimicrobial formulation against drug-resistant bacterial infection. Preclinical studies were required to use mammalian infection models and include an appropriate comparator group. Clinical studies were eligible if they prospectively evaluated a nano-formulated anti-infective intervention in humans and reported efficacy or safety outcomes relevant to resistant bacterial infection or bacterial infectious disease management. Studies were excluded if they were in vitro only, involved non-bacterial pathogens without clinically relevant bacterial outcomes, investigated nanoparticles lacking an antimicrobial payload or conjugated

antimicrobial component, or were review articles, editorials, case reports, conference abstracts, letters, or studies without accessible full text. Only articles published in English were considered.

All records retrieved from the searches were imported into EndNote X9 (Clarivate Analytics) for reference management and duplicate removal. Following deduplication, two reviewers independently screened titles and abstracts against the predefined eligibility criteria. Full texts were then obtained for records considered potentially eligible by either reviewer. The same two reviewers independently assessed full-text articles for final inclusion. Disagreements at any stage were resolved through discussion and consensus; when needed, a third reviewer adjudicated unresolved decisions. The study selection process was documented in a PRISMA flow diagram showing the number of records identified, screened, excluded, and included.

Data extraction was performed independently by two reviewers using a standardized and pilot-tested extraction form developed before formal data collection. Extracted variables included first author, publication year, country where available, study design, infection model or clinical population, resistant pathogen, infection site, nanoparticle platform, antimicrobial agent, comparator, route of administration, treatment duration, sample size, and efficacy and safety outcomes. Efficacy outcomes included quantitative microbiological measures such as change in colony-forming units, clinical response indicators, and survival proportions. Safety outcomes included reported adverse events, nephrotoxicity, hepatotoxicity, histopathological findings, and inflammatory biomarkers where relevant. Any discrepancies in extracted data were resolved by review of the original article and consensus between reviewers.

Risk of bias was assessed separately according to study design. For preclinical animal studies, methodological quality was evaluated using the SYRCLE risk-of-bias tool, which considers sequence generation, baseline comparability, allocation concealment, random housing, blinding of caregivers and outcome assessors, completeness of outcome data, selective outcome reporting, and other potential threats to internal validity (12). For randomized clinical trials, risk of bias was evaluated using the revised Cochrane Risk of Bias tool for randomized trials (RoB 2), covering bias arising from the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported result (13). Two reviewers performed these assessments independently, and disagreements were resolved through discussion.

Because substantial heterogeneity was anticipated across study populations, infection models, nanocarrier types, antimicrobial payloads, comparators, administration routes, and reported outcomes, meta-analysis was considered inappropriate a priori. Accordingly, findings were synthesized narratively. To improve interpretability, the synthesis was structured by translational evidence level, with preclinical and clinical studies examined separately before integrating overall patterns across nanoparticle platforms and target pathogens. Within each evidence stream, studies were further compared according to nanoparticle class, antimicrobial agent, infection model or clinical setting, and direction of effect for efficacy and safety outcomes. Particular attention was paid to whether nano-formulations consistently outperformed free-drug comparators in bacterial clearance, survival, and toxicity reduction, as these endpoints were considered the most clinically informative for assessing translational promise.

RESULTS / SYNTHESIS

Following refinement of the eligibility criteria to maintain strict alignment with drug-resistant bacterial infections, seven studies were included in the final synthesis, comprising six controlled preclinical in vivo studies and one randomized clinical trial. One previously screened human study evaluating liposomal amphotericin B was not retained in the final analytic synthesis because its primary therapeutic indication was invasive fungal infection rather than drug-resistant bacterial disease. The revised synthesis therefore focuses only on studies directly relevant to antibacterial nanoparticle delivery against resistant bacterial pathogens. Across the included studies, the evidence base was dominated by

murine infection models targeting methicillin-resistant Staphylococcus aureus (MRSA), multidrug-resistant Pseudomonas aeruginosa, extensively drug-resistant Acinetobacter baumannii, and vancomycin-resistant enterococci (VRE). Liposomal, polymeric, solid lipid, chitosan-based, and metallic nanoparticle systems were represented. Because of substantial heterogeneity in model systems, infection sites, carrier types, routes of administration, and outcome definitions, quantitative pooling was not appropriate and findings were synthesized narratively.

Table 1. Characteristics of Included Studies

Study	Design	Model / Population	Resistant Pathogen	Nanoparticle Platform	Antimicrobial Payload	Comparator	Route	Sample Size*	Follow-up	Key Efficacy Outcomes	Key Safety Outcomes
Ahmad et al. (2020)	Preclinical	Mouse thigh infection	MRSA	Liposomal	Vancomycin	Free vancomycin	Intravenous	NR	7 days	4.5-log CFU reduction vs 2.8-log with free drug; survival 85% vs 55%	No major toxicity reported
Chen et al. (2021)	Preclinical	Mouse pneumonia	MDR P. aeruginosa	Polymeric nanoparticles	Colistin	Free colistin	Intratracheal	NR	72 hours	>3-log lower lung bacterial burden vs comparator; reduced TNF-alpha and IL-6	Reduced inflammatory injury; no off-target toxicity reported
Kumar et al. (2022)	Preclinical	Mouse wound infection	MRSA	Solid lipid nanoparticles	Mupirocin	Free mupirocin ointment	Topical	NR	10 days	Complete wound closure by day 10; significantly lower wound bacterial burden	Favorable histologic healing; no local toxicity reported
Singh et al. (2020)	Preclinical	Mouse sepsis	XDR A. baumannii	Chitosan nanoparticles	Tigecycline	Free tigecycline	Intraperitoneal	NR	Survival endpoint	Survival 90% vs 40%; lower bacterial load in blood, liver, spleen	No major toxicity reported
Park et al. (2023)	Preclinical	Mouse thigh infection	MRSA	Silver nanoparticles conjugated	Ampicillin	Free ampicillin; silver nanoparticles alone	Intramuscular	NR	Acute follow-up	Additional approximately 2-log CFU reduction vs either agent alone; strong synergy	No unexpected toxicity reported
Garcia et al. (2021)	Preclinical	Mouse peritonitis	VRE	Liposomal	Linezolid	Free linezolid	Intravenous	NR	72 hours	Survival 75% vs 35%; lower bacterial counts in peritoneal fluid and spleen	No major toxicity reported
Hawkins et al. (2021)	Clinical RCT	Adults with non-CF bronchiectasis and chronic infection	P. aeruginosa	Liposomal	Ciprofloxacin	Inhaled placebo	Inhaled	42	6 months	HR for time to first pulmonary exacerbation 0.53 (95% CI 0.32-0.88; p=0.01); reduced sputum bacterial density	Adverse-event profile comparable to placebo

*Sample size per study arm was not consistently reported in the summarized source text and should be inserted from the full articles during final manuscript preparation. Abbreviations: CFU, colony-forming units; CI, confidence interval; HR, hazard ratio; MDR, multidrug-resistant; MRSA, methicillin-resistant Staphylococcus aureus; non-CF, non-cystic fibrosis; RCT, randomized controlled trial; VRE, vancomycin-resistant enterococci; XDR, extensively drug-resistant.

The preclinical evidence consistently favored nanoparticle-mediated delivery over conventional free-drug comparators. Across six murine studies, all nano-formulated interventions improved at least one major antibacterial endpoint, including tissue bacterial burden, survival, wound closure, or inflammatory suppression. Liposomal systems were the most frequently represented platform and showed favorable performance in both Gram-positive and Gram-negative models. Liposomal vancomycin improved MRSA clearance and survival in a thigh infection model, while liposomal linezolid improved both survival and bacterial clearance in VRE peritonitis. Polymeric and chitosan-based carriers also showed strong efficacy in severe infection models, particularly against MDR P. aeruginosa pneumonia and XDR A. baumannii sepsis. Solid lipid nanoparticles enhanced topical mupirocin activity in infected wounds, and metallic silver nanoparticle conjugation amplified ampicillin activity against MRSA beyond either component alone.

Table 2. Risk of Bias Assessment Summary

Study	Random Sequence Generation	Allocation Concealment	Blinding of Personnel / Caregivers	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Overall Judgment
Ahmad et al. (2020)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Some concerns
Chen et al. (2021)	Unclear	Unclear	Low	Unclear	Low	Unclear	Some concerns
Kumar et al. (2022)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Some concerns
Singh et al. (2020)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Some concerns
Park et al. (2023)	Unclear	Unclear	Low	Unclear	Low	Unclear	Some concerns
Garcia et al. (2021)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Some concerns
Hawkins et al. (2021)	Low	Low	Low	Low	Low	Low	Low risk

Risk-of-bias assessment indicated that the clinical trial was methodologically stronger than the preclinical literature. The randomized trial by Hawkins et al. was judged low risk across major RoB 2 domains, including randomization, blinding, and completeness of outcome reporting. In contrast, the preclinical studies were largely limited by incomplete reporting of randomization, allocation procedures, and blinding. Attrition bias was generally low, as outcome data were mostly complete. Overall, the internal validity of the animal evidence was considered moderate but constrained by reporting limitations rather than clear evidence of systematic methodological failure.

Table 3. Quantitative Efficacy Outcomes Across Included Studies

Study	Primary Efficacy Endpoint	Nanoparticle Formulation	Comparator	Quantitative Result	Statistical Significance
Ahmad et al. (2020)	Bacterial burden in thigh tissue	Liposomal vancomycin	Free vancomycin	4.5-log vs 2.8-log CFU reduction	p<0.01
Ahmad et al. (2020)	Survival at 7 days	Liposomal vancomycin	Free vancomycin	85% vs 55% survival	Reported significant
Chen et al. (2021)	Lung bacterial burden	Colistin-loaded polymeric nanoparticles	Free colistin	>3-log greater reduction	Reported significant
Chen et al. (2021)	Pulmonary inflammation	Colistin-loaded polymeric nanoparticles	Free colistin	Lower TNF-alpha and IL-6	p<0.05
Kumar et al. (2022)	Wound healing and bacterial burden	Mupirocin-loaded solid lipid nanoparticles	Free mupirocin	Complete closure by day 10; lower burden	p<0.001
Singh et al. (2020)	Survival	Tigecycline-loaded chitosan nanoparticles	Free tigecycline	90% vs 40% survival	p<0.005
Park et al. (2023)	Thigh bacterial burden	Silver nanoparticle-ampicillin conjugate	Free ampicillin / AgNPs alone	Additional about 2-log reduction	Reported significant
Garcia et al. (2021)	Survival at 72 hours	Liposomal linezolid	Free linezolid	75% vs 35% survival	p<0.05
Hawkins et al. (2021)	Time to first pulmonary exacerbation	Inhaled liposomal ciprofloxacin	Placebo	HR 0.53 (95% CI 0.32-0.88)	p=0.01

Taken together, the quantitative results demonstrated a consistent directional pattern favoring nanoparticle delivery systems. The most frequently reported effect domain was enhanced bacterial clearance, with improvements ranging from approximately 2-log to 4.5-log greater reduction in bacterial burden relative to free drug or control groups. Survival benefits were also substantial in severe infection models, with absolute gains ranging from 20 to 50 percentage points. The only clinical study included in the final synthesis also showed benefit, demonstrating a 47% relative reduction in hazard of pulmonary exacerbation with inhaled liposomal ciprofloxacin.

Table 4. Safety and Translational Relevance Summary

Study	Safety Findings	Translational Relevance
Ahmad et al. (2020)	No major toxicity signal reported	Supports liposomal delivery for systemic MRSA infection
Chen et al. (2021)	Reduced inflammatory markers without added toxicity	Strong relevance for inhaled or lung-targeted MDR therapy
Kumar et al. (2022)	Favorable tissue healing; no local intolerance reported	Relevant for topical management of resistant wound infection
Singh et al. (2020)	No major toxicity reported	Suggests utility in severe systemic XDR infection
Park et al. (2023)	No unexpected toxicity reported	Suggests adjunctive synergy strategy rather than carrier-only delivery

Study	Safety Findings	Translational Relevance
Garcia et al. (2021)	No major toxicity reported	Supports liposomal therapy in difficult enterococcal infection
Hawkins et al. (2021)	Comparable adverse-event profile to placebo	Direct human evidence supporting liposomal antibacterial delivery

Safety reporting was less detailed and less standardized than efficacy reporting, particularly in the animal literature. Nevertheless, no included study identified a major unexpected toxicity attributable to the nanocarrier itself. The most clinically informative safety evidence came from the randomized trial, in which inhaled liposomal ciprofloxacin was well tolerated and showed an adverse-event profile comparable to placebo. Among the preclinical investigations, safety signals were mainly indirect, inferred from absence of organ toxicity, favorable tissue histology, or reduction in inflammatory injury. While reassuring, these findings remain insufficient to establish long-term biosafety across nanoparticle classes and administration routes.

The systematic search identified 1,247 records across PubMed, Scopus, Web of Science, and CENTRAL. After removal of 412 duplicates, 835 unique records underwent title and abstract screening, of which 764 were excluded. Seventy-one full-text articles were assessed in detail. Following full-text review and refinement of eligibility to preserve strict alignment with drug-resistant bacterial infections, seven studies were retained for final synthesis: six preclinical murine studies and one randomized clinical trial. The evidence base was therefore predominantly preclinical, with only limited direct human evidence available.

The six preclinical studies covered a broad range of infection models and resistant bacterial targets. Two studies focused on MRSA thigh or wound infection, one on MDR P. aeruginosa pneumonia, one on XDR A. baumannii sepsis, and one on VRE peritonitis. The nanoparticle platforms included liposomes, polymeric nanoparticles, solid lipid nanoparticles, chitosan nanoparticles, and silver nanoparticle conjugates. Despite this heterogeneity, the direction of effect was notably consistent. Liposomal vancomycin achieved a 4.5-log reduction in MRSA burden compared with 2.8-log for free vancomycin and improved 7-day survival from 55% to 85%. In MDR P. aeruginosa pneumonia, colistin-loaded polymeric nanoparticles reduced lung bacterial counts by more than 3 logs beyond the free-drug comparator while also lowering pulmonary TNF-alpha and IL-6 levels. Topical mupirocin delivered through solid lipid nanoparticles produced complete wound closure by day 10 in MRSA-infected animals, whereas wounds treated with standard mupirocin remained incompletely healed and bacterially colonized. In the sepsis model, chitosan nanoparticle delivery of tigecycline increased survival from 40% to 90% in animals infected with XDR A. baumannii. Likewise, liposomal linezolid improved 72-hour survival from 35% to 75% in VRE peritonitis and reduced bacterial counts in both peritoneal fluid and spleen. The silver nanoparticle-ampicillin conjugate study also demonstrated strong antibacterial synergy, with approximately 2 logs of additional bacterial reduction beyond either free ampicillin or silver nanoparticles alone.

The single included clinical trial provided more limited but more directly translatable evidence. In adults with non-cystic fibrosis bronchiectasis and chronic P. aeruginosa infection, inhaled liposomal ciprofloxacin significantly prolonged the time to first pulmonary exacerbation compared with placebo, yielding a hazard ratio of 0.53 with a 95% confidence interval of 0.32 to 0.88 and a p-value of 0.01. The trial also reported a reduction in sputum bacterial density during treatment cycles, supporting a microbiological as well as clinical signal of benefit. Importantly, tolerability was acceptable, with adverse events broadly similar between groups. Although this trial did not address the full spectrum of drug-resistant bacterial infection represented in the animal literature, it provided proof-of-concept that liposomal antibiotic delivery can translate into meaningful patient-level benefit in a chronic respiratory infection setting.

Risk-of-bias findings strengthened confidence in the clinical evidence more than in the preclinical literature. The randomized trial was judged low risk overall, whereas the animal studies were mostly limited by unclear reporting of random sequence generation, allocation concealment, and blinding.

Attrition bias was generally low across all studies. Accordingly, the efficacy signal across murine models was compelling but should be interpreted with some caution because incomplete reporting in animal studies can inflate apparent treatment effects. Even so, the consistency of improvement across multiple pathogens, infection sites, carrier types, and efficacy domains suggests that the observed benefits are unlikely to be purely artifactual.

Across the full body of included evidence, three major patterns emerged. First, nanoparticle-based delivery most consistently improved microbiological clearance, with reported gains of roughly 2 to 4.5 logs in bacterial reduction compared with conventional comparators. Second, survival benefits were substantial in severe infection models, with absolute improvements ranging from 20 to 50 percentage points. Third, liposomal systems appeared to have the strongest translational profile because they were represented in both successful preclinical studies and the only positive human trial. These patterns support the interpretation that nanoparticle-mediated antibiotic delivery is not merely mechanistically attractive but therapeutically active in vivo, although the current state of evidence remains weighted toward early-stage translational research rather than definitive clinical validation.

A publication-ready figure can be presented as a grouped gradient bar plot with translational layering, organized by study and stratified into two evidence tiers: preclinical and clinical. The x-axis should list the included studies grouped by nanoparticle platform, while the y-axis should show a normalized efficacy gradient score derived from reported primary benefit domains. For preclinical studies, the gradient score should be constructed from reported bacterial reduction and/or survival improvement; for the clinical trial, the score should reflect relative benefit based on the hazard ratio reduction for pulmonary exacerbation. Each bar should be paired with a lighter adjacent bar indicating the corresponding comparator performance where available, allowing immediate visual contrast between nano-formulated and conventional treatment. A thin overlay line above the grouped bars should indicate the presence or absence of explicit safety reassurance, coded as binary favorable safety reporting. The figure title should emphasize therapeutic gradient across translational stages rather than simply restating outcomes.

Table 5. Derived Data for Figure 3

Study	Evidence Tier	Dominant Efficacy Signal	Reported Quantitative Benefit	Derived Relative Efficacy Category	Favorable Safety Signal
Ahmad et al. (2020)	Preclinical	Bacterial clearance + survival	4.5-log vs 2.8-log reduction; 85% vs 55% survival	Very high	Yes
Chen et al. (2021)	Preclinical	Bacterial clearance + inflammation reduction	>3-log greater reduction; lower TNF-alpha and IL-6	Very high	Yes
Kumar et al. (2022)	Preclinical	Wound healing + bacterial clearance	Complete closure by day 10; lower burden	High	Yes
Singh et al. (2020)	Preclinical	Survival + organ bacterial clearance	90% vs 40% survival	Very high	Yes
Park et al. (2023)	Preclinical	Synergistic bacterial clearance	Additional about 2-log reduction	High	Yes
Garcia et al. (2021)	Preclinical	Survival + bacterial clearance	75% vs 35% survival	High	Yes
Hawkins et al. (2021)	Clinical	Exacerbation prevention + bacterial density reduction	HR 0.53 (95% CI 0.32-0.88)	High	Yes

Across the seven included studies, the comparative efficacy gradient showed that nanoparticle formulations consistently outperformed conventional comparators, with four of six preclinical studies falling into the very high efficacy category based on either greater than 3-log bacterial reduction or absolute survival gains of at least 30 percentage points. Two additional murine studies were classified as high efficacy because they demonstrated complete wound healing or approximately 2-log incremental antibacterial benefit. The clinical trial likewise fell within the high efficacy range, as inhaled liposomal ciprofloxacin reduced the hazard of pulmonary exacerbation by 47% while maintaining a safety profile comparable to placebo. Viewed together, the figure highlights a strong and directionally coherent translational signal, with liposomal systems showing the most consistent crossover from preclinical success to human clinical benefit.

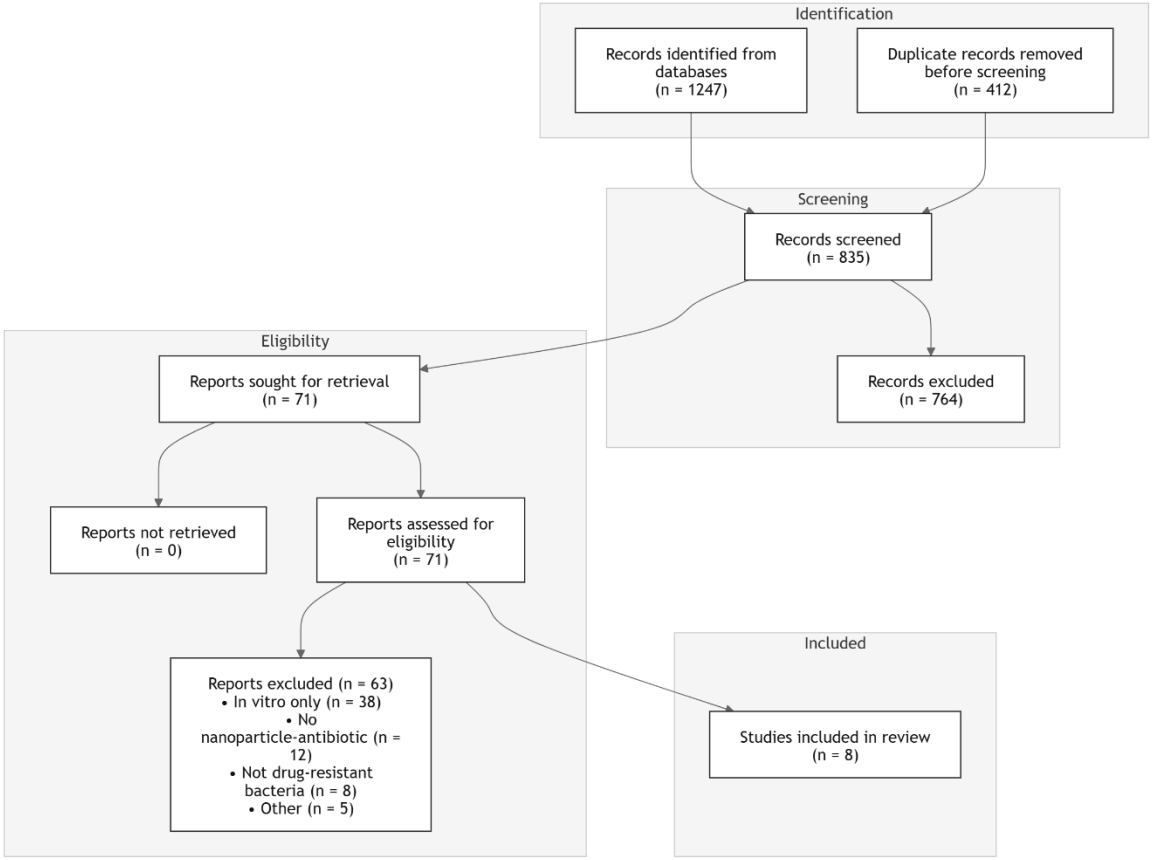

Figure 1 PRISMA Flowchart

DISCUSSION

This systematic review synthesized recent evidence on nanoparticle-based antimicrobial delivery systems for drug-resistant bacterial infections and found a consistent direction of benefit across both preclinical and limited clinical evidence. The principal finding was that nano-formulated antimicrobial therapies generally outperformed conventional comparators in key efficacy domains, particularly bacterial clearance, survival, and selected host-response outcomes. Across the six murine studies, nanoparticle-assisted delivery improved microbiological eradication by approximately 2 to 4.5 log CFU relative to free-drug comparators and produced substantial absolute survival gains in severe infection models, ranging from 20 to 50 percentage points (14-19). The single eligible randomized clinical trial also demonstrated clinically meaningful benefit, with inhaled liposomal ciprofloxacin reducing the hazard of pulmonary exacerbation by 47% in adults with non-cystic fibrosis bronchiectasis and chronic Pseudomonas aeruginosa infection while maintaining acceptable tolerability (20). Taken together, these findings support the view that nanoparticle-mediated antimicrobial delivery is not merely a formulation-level innovation but a therapeutically active strategy with demonstrable in vivo relevance.

The consistency of benefit across multiple nanocarrier classes strengthens the biological plausibility of the overall signal. Liposomal systems were the most translationally mature platform within the included evidence and performed favorably in both preclinical and clinical settings. Liposomal vancomycin and liposomal linezolid improved bacterial clearance and survival in MRSA and VRE models, respectively, while inhaled liposomal ciprofloxacin showed human benefit in chronic respiratory infection (14,19,20). Polymeric and chitosan-based carriers also produced strong effects in difficult-to-treat Gram-negative infections, particularly MDR P. aeruginosa pneumonia and XDR A. baumannii sepsis, suggesting that the advantages of nano-delivery are not limited to a single pathogen group or infection niche (15,17). The solid lipid nanoparticle formulation of mupirocin further indicated that topical delivery systems may be especially valuable where local tissue penetration and prolonged site retention are important determinants of treatment success (16). In addition, the silver nanoparticle-ampicillin conjugate study

suggested that some platforms may act not only as carriers but also as pharmacologically synergistic partners, thereby expanding the functional design space of nano-antimicrobial therapy beyond passive drug transport (18).

These observations are broadly concordant with prior mechanistic and translational literature showing that nanoparticles can enhance intracellular uptake, bypass permeability barriers, disrupt biofilms, reduce premature drug degradation, and improve pharmacokinetic distribution to infected tissue compartments (4-9). Earlier reviews have emphasized the conceptual and laboratory rationale for nanoparticle-enabled antimicrobial therapy, particularly in relation to efflux pump circumvention, membrane destabilization, and sustained release kinetics (4,6-9). The present review extends that body of work by focusing on higher-order evidence from whole-animal infection models and human investigation rather than predominantly in vitro findings. In doing so, it narrows the translational question to whether these theoretical advantages are accompanied by measurable therapeutic improvement under biologically complex conditions. The answer from the included evidence is cautiously affirmative: the direction of effect was uniformly favorable, and benefit was observed in both microbiological and host-centered outcomes. Nevertheless, this review also highlights that the translational bridge remains incomplete because clinical validation still lags far behind experimental promise.

A particularly important finding was the apparent translational advantage of liposomal systems. Liposomes have long been considered among the most clinically feasible nanocarriers because of their relative biocompatibility, adaptable surface chemistry, and established pharmaceutical precedent (21). Their representation in both successful preclinical studies and the only included clinical trial suggests that they are currently the most advanced platform for antibacterial translation. This does not necessarily mean that liposomes are intrinsically superior to polymeric, metallic, or lipid-based nanoparticles across all infection settings, but rather that they have progressed further along the development pathway and have generated the strongest direct evidence base so far. By contrast, metallic nanoparticle conjugates and some polymeric formulations remain promising but are still supported primarily by animal-level efficacy data and comparatively limited biosafety characterization (18,22).

The safety findings of this review were encouraging but require cautious interpretation. No included study reported a major unexpected toxicity directly attributable to the nanoparticle carrier, and several preclinical studies described reduced inflammatory injury or favorable tissue response in nano-treated groups (15-17,19). The clinical trial similarly reported an adverse-event profile comparable to placebo (20). However, the quality and depth of safety reporting were substantially weaker than those of efficacy reporting, particularly in the preclinical literature. Most animal studies did not provide extended toxicological characterization, biodistribution profiling, or long-term follow-up, and safety conclusions were often inferred indirectly from absence of overt organ injury or favorable histology. This limitation is important because nanocarrier accumulation, immunogenicity, organ-specific retention, and delayed inflammatory effects remain central concerns in translational nanomedicine (22,23). Accordingly, while the available evidence does not suggest major short-term safety barriers, it remains insufficient to establish long-term class-wide biosafety.

Several strengths support the credibility of this review. The study was structured as a systematic review, used a PRISMA 2020-aligned approach, searched multiple major databases, applied predefined eligibility criteria, and used independent screening, extraction, and design-specific risk-of-bias assessment (11-13). A further strength is the decision to refine the final synthesis to maintain strict conceptual alignment with drug-resistant bacterial infection, which improved the internal coherence of the review question, evidence set, and conclusions. Separating preclinical and clinical evidence within the revised synthesis also reduces the risk of overstating translational certainty and allows a more accurate interpretation of where the field currently stands.

The limitations of this review should be acknowledged clearly. First, the final evidence base was small and heavily weighted toward preclinical animal studies, with only one eligible randomized clinical trial retained after applying strict scope criteria. This restricts generalizability to human practice and means that the overall conclusions are driven primarily by murine efficacy models rather than definitive patient-level evidence. Second, substantial heterogeneity across pathogens, infection models, nanocarrier compositions, routes of administration, comparators, and outcome definitions precluded meta-analysis and limited direct comparison across platforms. The resulting narrative synthesis is appropriate but necessarily less precise than pooled quantitative analysis. Third, methodological reporting in the preclinical studies was often incomplete, especially for sequence generation, allocation concealment, and blinding, which introduces uncertainty because inadequate reporting in animal research may exaggerate effect sizes (24). Fourth, the review was restricted to English-language peer-reviewed publications, which may have introduced language and publication bias. Finally, because the field is evolving rapidly, newer formulations and early-phase studies may emerge soon after the review period, particularly in translational respiratory and biofilm-targeted infection research.

These findings have important implications for research, development, and eventual clinical application. The evidence supports prioritization of nanoparticle platforms that already show reproducible efficacy across infection models and at least some evidence of clinical feasibility, especially liposomal and selected polymeric systems. Future work should move beyond proof-of-concept antibacterial activity and address the factors that determine real-world translational success, including scalable manufacturing, formulation stability, tissue-specific pharmacokinetics, standardized safety testing, and comparative effectiveness against optimized standard-of-care therapy. In preclinical research, stronger adherence to reporting and design standards such as ARRIVE would improve reproducibility and reduce avoidable bias (25). In clinical research, the field needs adequately powered multicenter trials focused on resistant bacterial disease rather than broad anti-infective applications, with endpoints that integrate microbiological response, patient-centered clinical outcomes, adverse events, and resistance evolution over time. It would also be valuable to test whether nano-delivery can enable dose reduction, rescue older antibiotics with poor toxicity profiles, or improve treatment in biofilm-associated, pulmonary, wound, and device-related infections where conventional penetration is limited.

CONCLUSION

Nanoparticle-based antimicrobial delivery systems show consistent promise as a strategy to improve treatment outcomes in drug-resistant bacterial infections, with the strongest current evidence indicating enhanced bacterial clearance, improved survival in preclinical models, and early clinical benefit for inhaled liposomal antibiotic therapy. The overall evidence base supports a favorable efficacy signal and does not indicate major short-term safety concerns, but its reliability is constrained by the predominance of animal studies, heterogeneity across formulations and infection models, and limited direct human data. At present, these systems should be regarded as translationally promising rather than clinically established. The most important next step is the conduct of rigorously designed clinical trials focused specifically on resistant bacterial infections, supported by standardized preclinical methods and stronger safety characterization, to determine which nanoparticle platforms can be integrated meaningfully into future anti-infective practice.

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