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Research paper

Plasmid-Mediated Antimicrobial Resistance in The Human Microbiome: A Scoping Review of Horizontal Gene Transfer During Antibiotic Exposure

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Abstract

Background: AMR remains a critical global health threat, yet pathogen-focused surveillance underestimates the commensal human microbiome as a resistance gene reservoir. Evidence linking plasmid persistence, stress-associated mobilization, and clinical relevance remains fragmented.
Objective: This scoping review synthesized evidence on plasmid persistence mechanisms, antibiotic- and stressor-associated horizontal gene transfer (HGT), and clinical or translational implications of microbiome-associated AMR.
Methods: Following PRISMA-ScR guidelines, five databases (PubMed/MEDLINE, Embase, Web of Science, Scopus, and Global Health) were searched for English-language studies published between January 2010 and December 2025. From 1,200 records identified, 223 unique records were screened after duplicate removal, and 35 met the inclusion criteria. Data were extracted on plasmid maintenance, mobilization pathways, clinical relevance, and translational approaches.
Results: Sixteen studies on plasmid persistence showed that maintenance may be supported by host–plasmid co-adaptation, compensatory evolution, regulatory remodeling, epistatic interactions, and stability systems. Eight studies on stressor-associated mobilization indicated that HGT may be influenced by SOS responses, metabolic disruption, redox imbalance, antibiotic-specific regulatory effects, and selection-driven genetic exchange. Eleven clinical or translational studies highlighted underdetection of plasmid-mediated AMR transmission and early evidence for microbiome-based and anti-plasmid strategies, including fecal microbiota transplantation, CRISPR-based targeting, conjugation inhibition, and RecA-targeted approaches.
Conclusion: Plasmid-mediated AMR in the human microbiome is shaped by persistence dynamics, stress-associated mobilization, and clinical selective pressures. Plasmid-resolved surveillance, standardized HGT detection, longitudinal studies, and validated microbiome-informed interventions are needed to strengthen AMR mitigation.

Keywords: *Antimicrobial Resistance; Plasmid Persistence; Horizontal Gene Transfer; Human Microbiome; Mobilome; Antibiotic Exposure.*

1. Introduction

1.1. Background

Antimicrobial resistance (AMR) is one of the major global health challenges of the 21st century. In 2019, bacterial AMR was associated with an estimated 4.95 million deaths worldwide, highlighting its substantial clinical and public health burden [1]. Current AMR surveillance and control strategies focus largely on clinically isolated pathogens, including Escherichia coli, Klebsiella pneumoniae, and Pseudomonas spp. Although this pathogen-focused approach is essential for diagnosis, treatment, and infection control, it may underestimate the

broader reservoir of resistance determinants present within the commensal human microbiome [2–4]. The human microbiome can act as a reservoir of antibiotic resistance genes (ARGs), some of which may be mobilized through horizontal gene transfer (HGT), thereby contributing to the dissemination of resistance across bacterial species and ecological niches [5–7].

Mobile genetic elements (MGEs), including conjugative plasmids, integrons, transposons, and integrative conjugative elements (ICEs), play important roles in HGT and can facilitate the spread of ARGs [8–12]. Although several classes of MGEs contribute to resistance dissemination, this review focuses primarily on plasmids, while considering other MGEs where they directly interact with or influence plasmid-mediated mobilization and persistence. Plasmids are particularly important because they can persist within bacterial populations despite imposing fitness costs on their hosts. This persistence may be supported by host–plasmid co-adaptation, compensatory mutations, epistatic interactions, and plasmid stability systems, which can promote plasmid maintenance even in the absence of continuous antibiotic selection [13–16].

Antibiotic exposure can further shape plasmid-mediated AMR dynamics by acting both as a selective pressure and as an ecological disturbance. In addition to selecting for resistant bacterial populations, antibiotic exposure may activate stress-responsive pathways that influence MGE mobilization. The SOS response, mediated through LexA-dependent regulation, has been implicated in the activation, excision, and transfer of certain MGEs under antibiotic-induced stress. In addition, metabolic and redox stress pathways may contribute to HGT through mechanisms that are partly independent of classical DNA damage responses [6], [11], [12], [17]. These processes can operate across multiple biological scales, from intracellular regulatory activation to community-level dissemination within human gut, environmental, and clinical microbial ecosystems [8], [18].

Clinical genomic surveillance studies increasingly suggest that plasmid-mediated AMR transmission may occur within and between patients, sometimes remaining undetected by conventional microbiological methods [2–4]. These findings highlight the potential contribution of the mobilome to the dissemination of healthcare-associated AMR. At the same time, emerging translational strategies have begun to explore ways to reduce reservoirs of resistance or to interrupt plasmid-mediated transmission. These include microbiome-based approaches, such as fecal microbiota transplantation (FMT), for decolonizing multidrug-resistant organisms, as well as preclinical strategies using CRISPR-Cas systems and plasmid-curing approaches to target plasmid maintenance or resistance determinants [19–23]. However, these approaches remain at different stages of development, and their broader clinical application is constrained by delivery challenges, safety concerns, ecological complexity, and limited generalizability.

The literature on plasmid persistence, antibiotic-triggered mobilization, and the clinical implications of microbiome-associated resistance is heterogeneous and fragmented across molecular, ecological, and translational domains [4], [10]. A scoping review is therefore appropriate for mapping the available evidence, identifying areas of convergence and uncertainty, and clarifying gaps in current understanding. Important evidence gaps include incomplete knowledge of plasmid persistence in commensal microbiota, variability in mobilization pathways under antibiotic and environmental stress, limited plasmid-resolved surveillance in clinical settings, and insufficient clinical evaluation of interventions targeting plasmids or the broader mobilome [19], [20], [23].

1.2. Review objectives

This scoping review aims to:

1) Map existing evidence on molecular mechanisms that support plasmid persistence in commensal microbiota.
2) Identify and categorize antibiotic- and stressor-associated molecular and ecological mechanisms that may influence plasmid-mediated HGT.
3) Chart reported clinical consequences and emerging intervention strategies related to microbiome-associated plasmid-mediated AMR.

1.3. Review questions

1) What molecular mechanisms supporting plasmid persistence in commensal bacteria have been reported?
2) How does antibiotic exposure influence plasmid mobilization across molecular, microbial community, and clinical contexts?
3) What clinical outcomes and translational strategies have been documented in relation to microbiome-associated plasmid-mediated AMR?

2. Methods

2.1. Search strategy

This scoping review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines [24]. The objective was to map the breadth, characteristics, and distribution of evidence relating to plasmid persistence, antibiotic- and stressor-associated mobilization of mobile genetic elements (MGEs), and the clinical and translational implications of plasmid-mediated antimicrobial resistance (AMR).

A comprehensive literature search was conducted across five electronic databases: PubMed/MEDLINE, Embase, Web of Science, Scopus, and Global Health. The search strategy combined controlled vocabulary terms, where applicable, such as MeSH and Emtree terms, with free-text keywords to maximize sensitivity and capture both mechanistic and translational studies.

The search framework was organized around four conceptual domains: genetic elements, resistance context, transfer mechanisms, and host or stress context. The following keyword groups were combined using Boolean operators:

- Genetic elements: “plasmid” OR “mobile genetic element” OR “MGE” OR “conjugative element.”
- Resistance context: “antimicrobial resistance” OR “antibiotic resistance” OR “resistome.”
- Transfer mechanisms: “horizontal gene transfer” OR “HGT” OR “conjugation” OR “mobilization.”
- Host and stress context: “microbiome” OR “gut microbiota” OR “commensal bacteria” OR “host-associated microbiota” AND “antibiotic exposure” OR “stress response” OR “SOS response” OR “oxidative stress.”

To enhance reproducibility, a representative PubMed/MEDLINE search string is provided below:

(“plasmid”[Title/Abstract] OR “mobile genetic element”[Title/Abstract] OR “MGE”[Title/Abstract] OR “conjugative element”[Title/Abstract])

AND (“antimicrobial resistance”[Title/Abstract] OR “antibiotic resistance”[Title/Abstract] OR “resistome”[Title/Abstract])

AND ("horizontal gene transfer"[Title/Abstract] OR "HGT"[Title/Abstract] OR "conjugation"[Title/Abstract] OR "mobilization"[Title/Abstract])
AND ("microbiome"[Title/Abstract] OR "gut microbiota"[Title/Abstract] OR "commensal bacteria"[Title/Abstract] OR "host-associated microbiota"[Title/Abstract])
AND ("antibiotic exposure"[Title/Abstract] OR "stress response"[Title/Abstract] OR "SOS response"[Title/Abstract] OR "oxidative stress"[Title/Abstract])
Equivalent search strategies were adapted for Embase, Web of Science, Scopus, and Global Health using database-specific syntax and indexing systems. The final search was conducted on 31 December 2025. Searches were limited to English-language publications published between January 2010 and December 2025. This period was selected to capture both foundational and contemporary evidence while maintaining a consistent search window. Backward citation tracking of included studies was also conducted to identify additional relevant articles not captured through the initial database searches.
A total of 1,200 records were identified, including 1,150 records through database searching and 50 additional records through other sources. After duplicate removal, 223 unique records remained for title and abstract screening. Following full-text assessment against the eligibility criteria, 35 studies were included in the final synthesis.

2.2. Study selection

All retrieved records were imported into a reference management system, and duplicates were removed before screening. Study selection was conducted in two sequential stages: title and abstract screening, followed by full-text assessment of potentially eligible articles. Screening was performed using predefined eligibility criteria aligned with the review objectives.
Studies were included if they met at least one of the following criteria:
1) Reported original experimental, observational, or clinical data on mechanisms of plasmid persistence.
2) Provided mechanistic or experimental evidence of antibiotic- or stressor-associated mobilization of plasmids or closely associated MGEs.
3) Reported clinical surveillance, interventional, or translational findings related to plasmid-mediated AMR or microbiome-associated resistance dissemination.

Primary empirical studies formed the main evidence base of the review. Selected mechanistic and narrative reviews were also included where they provided integrative, system-level insights into plasmid biology, MGE dynamics, or mobilome-associated AMR that could not be adequately captured through isolated primary studies. These review articles were not treated as equivalent to primary empirical studies. Instead, they were used to contextualize mechanisms, clarify conceptual links, and support interpretation where primary evidence was fragmented.
Studies were excluded if they:
- Did not address plasmids, MGEs, antimicrobial resistance, or horizontal gene transfer;
- Were purely conceptual without mechanistic, experimental, clinical, or translational grounding;
- Were conference abstracts, editorials, commentaries, or other non-peer-reviewed publications;
- Did not provide sufficient methodological detail to determine relevance to the review objectives;
- Were not published in English;
- Were published outside the January 2010 to December 2025 search window.

Full-text screening was conducted to confirm methodological relevance and alignment with the review objectives. The study selection process, including identification, duplicate removal, screening, eligibility assessment, and final inclusion, is summarized in the PRISMA-ScR flow diagram (Fig. 1).

2.3. Data extraction and synthesis

Data extraction was conducted using a standardized and piloted extraction framework to improve consistency and transparency across included studies. Extracted variables included author and year, country or region of study, study design, biological system or host organism, plasmid or MGE type, experimental or clinical context, reported fitness costs, compensatory mechanisms, mobilization triggers, evidence of horizontal gene transfer, and reported clinical or translational outcomes.
Methodological characteristics were also documented, including analytical approaches such as growth and competition assays, minimum inhibitory concentration (MIC) testing, transcriptomic and metabolomic profiling, whole-genome sequencing (WGS), long-read sequencing, population modelling, in vivo colonization models, clinical surveillance, and clinical outcome assessment. This allowed comparison of evidentiary depth and methodological heterogeneity across studies.
For analytical coherence, extracted data were organized into three domains aligned with the review objectives:
1) Plasmid persistence, defined as sustained maintenance of plasmids within bacterial host populations despite potential or observed fitness costs.
2) Plasmid or MGE mobilization, defined as activation, excision, transfer, or increased dissemination of plasmids or closely associated MGEs through mechanisms such as SOS response induction, stress-mediated transposition, conjugative transfer, transformation, or transduction.
3) Clinical and translational outcomes, including plasmid-mediated transmission in clinical settings, decolonization of multidrug-resistant organisms, reduction of resistance burden, and safety or efficacy signals associated with interventions such as FMT, CRISPR-based plasmid targeting, conjugation inhibition, plasmid-curing strategies, and pharmacological inhibition of plasmid-associated pathways.

Data extraction was performed independently by two reviewers to improve reliability. Discrepancies were resolved through discussion and, where necessary, adjudication by a third reviewer.
Given the methodological and contextual heterogeneity of the included studies, findings were synthesized using a structured narrative approach. The synthesis focused on identifying patterns of convergence, areas of divergence, and sources of inconsistency across studies. Differences in study design, biological context, methodological resolution, and scale of inference were explicitly considered. Particular attention was given to distinguishing between well-supported mechanistic evidence, context-dependent findings, and emerging or preliminary translational signals.

2.4. Evidence appraisal and evidence characterization

Consistent with PRISMA-ScR guidance and the exploratory purpose of scoping reviews, a formal risk-of-bias assessment was not undertaken [24]. The purpose of this review was to map the scope, characteristics, and distribution of available evidence rather than to generate pooled effect estimates or compare intervention effectiveness.

However, to strengthen interpretive rigor and address variation in evidentiary strength, a structured evidence characterization was conducted. Each included study was classified according to:

- Study design, such as experimental evolution, in vitro mechanistic study, in vivo model, clinical surveillance, interventional study, modelling study, mechanistic synthesis, or review-based synthesis;
- Biological context, such as laboratory-controlled system, animal model, human microbiome, healthcare setting, or environmental setting;
- Type of evidence generated, including mechanistic, observational, translational, or conceptual evidence.
- In addition, key methodological attributes relevant to evidentiary strength were documented, including:
- Use of high-resolution genomic approaches, such as WGS or long-read sequencing;
- Experimental validation of horizontal gene transfer events;
- Distinction between controlled experimental designs and observational designs;
- Scale of inference, including molecular, organismal, community, or clinical levels;
- Directness of evidence in relation to plasmid persistence, mobilization, or clinical transmission.

Rather than applying quantitative quality scores, studies were interpreted within their methodological and biological contexts. This approach allowed differentiation between high-confidence mechanistic findings, model-based or context-dependent inferences, and early-stage translational evidence.

The inclusion of heterogeneous study types, including selected narrative and mechanistic reviews, may introduce interpretive variability. However, this was considered appropriate for a scoping review designed to map a broad and interdisciplinary field. Where review articles were included, their role was explicitly contextualized and distinguished from primary empirical evidence during synthesis and interpretation.

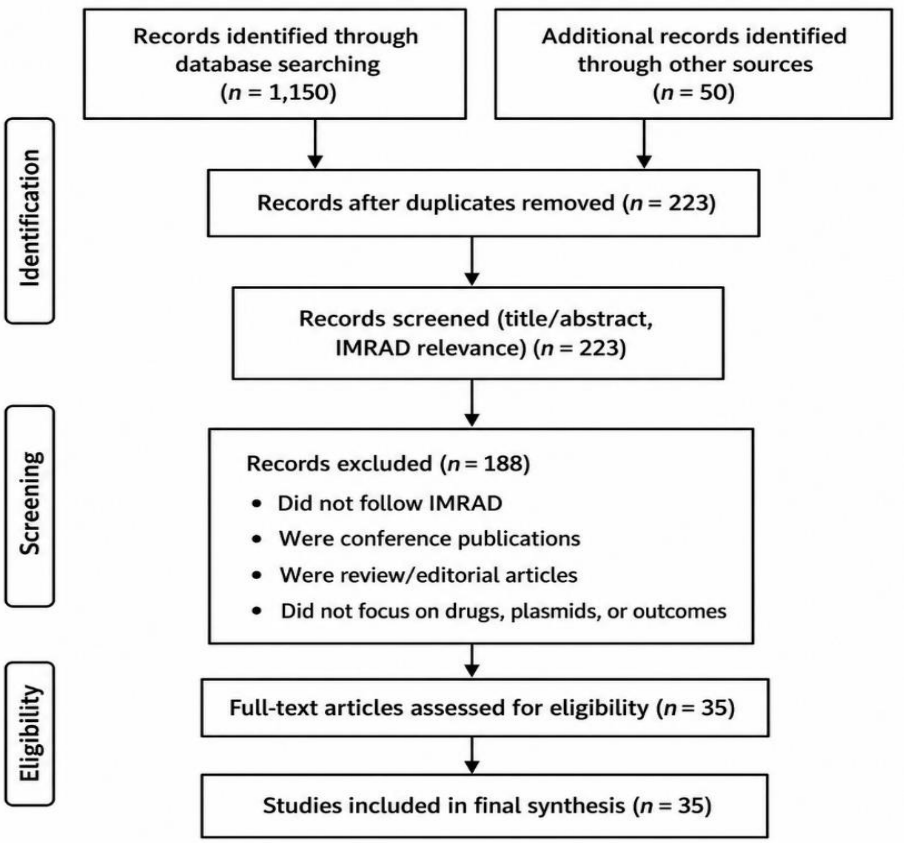

Fig. 1: PRISMA-Scr Flow Diagram of Study Identification, Screening, Eligibility Assessment, And Inclusion.

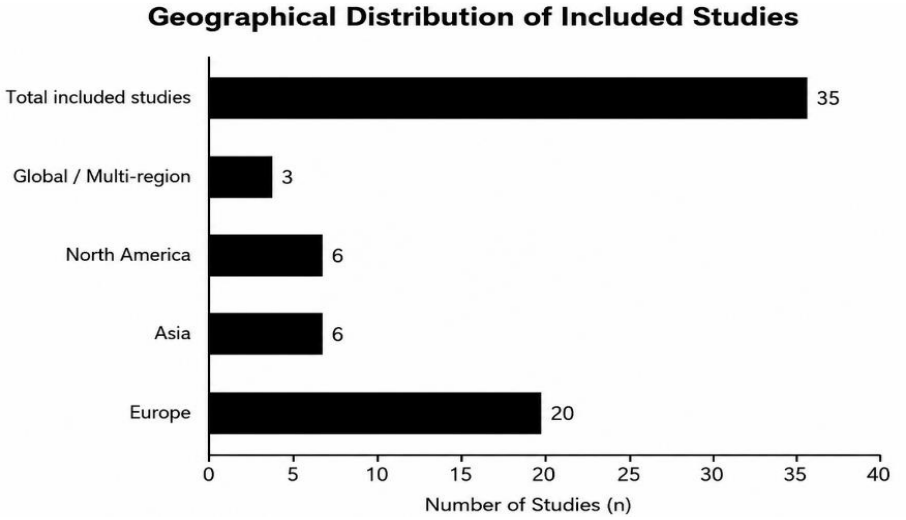

Fig. 2: Geographical Distribution of Included Studies.

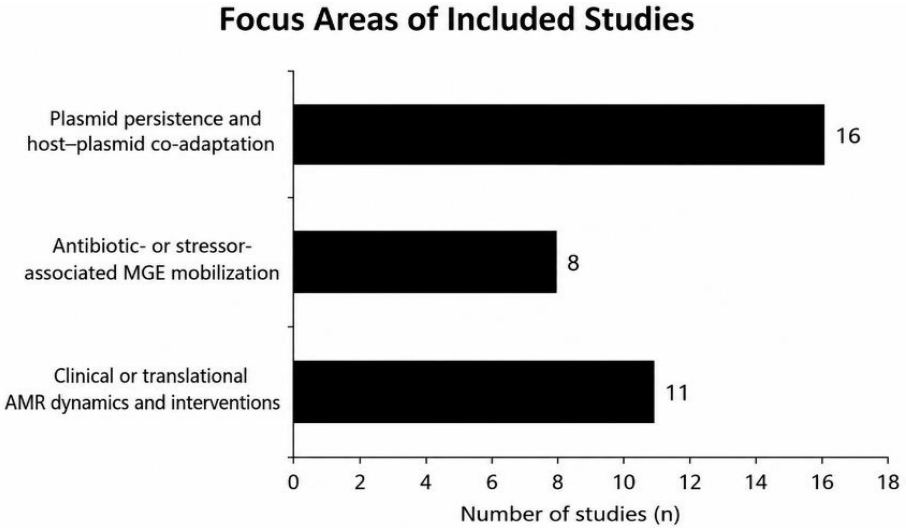

Fig. 3: Distribution of Study Focus Areas Across the Three Review Domains.

3. Results

A total of 1,200 records were identified, including 1,150 records through database searching and 50 additional records through other sources. After duplicate removal, 223 unique records remained for title and abstract screening. Following full-text assessment against the predefined eligibility criteria, 35 studies were included in the final synthesis (Fig. 1).

The geographical distribution of included studies was uneven (Fig. 2). Most studies originated from Europe (n = 20), followed by Asia (n = 6) and North America (n = 6), while multi-region or global studies accounted for three studies (n = 3). No included studies were identified from Africa or South America, and evidence from other underrepresented low- and middle-income regions was limited or absent. This uneven geographical representation may constrain the generalizability of findings across settings with different antimicrobial use patterns, healthcare systems, infection prevention capacity, microbiome exposures, and AMR burdens.

Methodologically, laboratory-based and experimental evolution studies represented the largest group of included studies and formed the main source of mechanistic evidence. These were complemented by clinical genomic surveillance studies, targeted mobilization experiments, multi-omic studies, modelling approaches, systematic or narrative syntheses, and preclinical intervention studies. This distribution indicates that the evidence base is strongest for controlled mechanistic studies, whereas clinical, ecological, and population-level evidence remains comparatively limited.

The included studies were organized into three thematic domains: plasmid persistence and host–plasmid co-adaptation (n = 16), antibiotic- or stressor-associated MGE mobilization (n = 8), and clinical or translational AMR dynamics and interventions (n = 11) (Fig. 3). These domains differed in evidentiary maturity. Persistence studies were generally supported by mechanistic and experimental evidence, mobilization studies were informative but heterogeneous, and clinical or translational studies were more variable in design and methodological resolution. This distinction is important when interpreting the strength and applicability of findings across the review.

3.1. Molecular mechanisms of plasmid persistence

Sixteen studies examined plasmid persistence and host–plasmid interactions (Table 1). Experimental evolution studies formed the dominant evidence base [10], [13], [25–30]. Additional evidence came from clinical or microbiome-associated experimental studies [14–16], [31], [33], modelling approaches [15], [34], and mechanistic or conceptual syntheses [5], [27], [32]. Together, these studies suggest that plasmid persistence is shaped by interactions among plasmid-associated fitness costs, compensatory adaptation, host genetic background, plasmid stability mechanisms, and ecological context.

Across the persistence studies, a consistent pattern was observed: plasmid maintenance was not determined solely by the initial fitness cost of plasmid carriage. Although several studies reported measurable fitness costs, the magnitude and persistence of these costs varied across bacterial hosts, plasmid types, and experimental settings. Experimental evolution studies showed that plasmids could be stabilized over time through compensatory adaptation, particularly under controlled laboratory conditions [25–31]. However, because many of these studies used simplified experimental systems, their findings should be interpreted cautiously when extrapolating to complex human microbiomes.

Compensatory evolution was the most frequently reported stabilizing mechanism. Chromosomal mutations were commonly identified in experimental evolution studies [25–31], while plasmid-level adaptations, including rearrangements and changes affecting plasmid–host compatibility, were reported less consistently [5], [10], [13]. Multi-omic and in vivo studies also highlighted regulatory, transcriptional, and metabolic remodeling as possible contributors to plasmid maintenance [16], [31]. These findings indicate that plasmid persistence may arise through multiple adaptive routes rather than a single universal mechanism.

A key area of variability concerned the relative contribution of host adaptation versus plasmid adaptation. Experimental evolution studies tended to emphasize host genomic compensation [25–31], whereas modelling and microbiome-associated studies suggested that plasmid evolution, host phylogeny, global epistasis, and ecological structure may also influence persistence [15], [32–34]. This remains an important unresolved issue because laboratory systems may not fully capture the selective pressures, spatial structure, and multispecies interactions present in natural microbial communities.

The taxonomic distribution of persistence studies was also uneven. Most studies focused on model or clinically familiar organisms, particularly Escherichia coli and Pseudomonas spp. [10], [16], [25–30]. Fewer studies examined more diverse or ecologically complex systems, including gut-associated Enterobacteriaceae [15], [33], Shewanella oneidensis [13], and Haemophilus influenzae [31]. This taxonomic concentration limits the ecological breadth of current evidence and suggests that plasmid persistence in less-studied commensal taxa remains insufficiently characterized.

Plasmid loss was reported infrequently and was generally associated with delayed or absent compensatory adaptation [10,26]. Once compensatory changes occurred, plasmid maintenance was often stabilized, particularly in experimental systems. However, this should not be interpreted as evidence that all resistance plasmids persist indefinitely in natural microbiomes. Instead, the findings suggest that plasmid persistence is more likely when compensatory adaptation, plasmid stability systems, host compatibility, or ecological conditions reduce the burden of plasmid carriage.

Evidence of horizontal gene transfer (HGT) was directly reported in several persistence studies [10], [13–16], [30], [33], [34], although transfer frequencies varied across systems. Laboratory studies generally provided clearer evidence of transfer, whereas in vivo and clinically relevant contexts showed more variable or less directly measured transfer dynamics. This difference suggests that experimental systems may overestimate the frequency or efficiency of plasmid transfer compared with natural microbial communities.

Overall, the evidence supports a context-dependent model in which plasmid persistence is promoted by compensatory evolution, host–plasmid compatibility, plasmid stability mechanisms, and ecological conditions. However, the predominance of laboratory-based evidence, limited taxonomic diversity, and variability in HGT measurement restrict the generalizability of any single mechanistic explanation.

Table 1: Molecular Mechanisms of Plasmid Persistence

Study	Country/region	Study type	Bacterial system	Plasmid/MGE	Main persistence mechanism	HGT reported	Key limitation
Harrison et al., 2015 [25]	United Kingdom	Experimental evolution	Pseudomonas fluorescens	pQBR plasmid	Chromosomal compensatory mutations supporting plasmid stability	No	Laboratory system; limited ecological complexity
Loftie-Eaton et al., 2016 [10]	United Kingdom	Experimental evolution	Escherichia coli	Conjugative plasmids	Host mutations and plasmid rearrangements supporting host–plasmid co-adaptation	Yes	Controlled laboratory setting
Vogwill et al., 2016 [26]	United Kingdom	Experimental evolution	Pseudomonas spp.	Small non-conjugative plasmids	Chromosomal compensation reduces plasmid-associated fitness cost	No	Limited to selected bacterial backgrounds
Hall et al., 2017 [27]	United Kingdom	Evolutionary synthesis	Plasmid-bearing bacterial populations	Conjugative and non-conjugative plasmids	Conceptual comparison of infectious transmission and compensatory evolution as routes to plasmid stability	Indirect	Review-based; not a primary experimental study
Yano et al., 2016 [30]	Japan	Experimental evolution	E. coli	IncP-1 plasmids	Host–plasmid adaptation reducing plasmid burden	Yes	Limited environmental complexity
Stalder et al., 2017 [13]	Switzerland	Experimental evolution	Shewanella oneidensis MR-1	IncP-1β pBP136Km	Plasmid and host changes supporting vertical transmission	Yes	Single-species experimental system
San Millán, 2018 [5]	Spain	Mechanistic review	Clinical AMR contexts	Resistance plasmids	Synthesis of plasmid-mediated AMR evolution and persistence mechanisms	Indirect	Review-based; not a primary experimental study
Hall et al., 2020 [29]	United Kingdom	Experimental evolution	Pseudomonas spp.	Large plasmids	Rapid amelioration of plasmid fitness costs through diverse compensatory pathways	No	Laboratory-based inference
Alonso-del Valle et al., 2021 [15]	Spain	Experimental and modelling study	Human gut Enterobacteriaceae	IncL pOXA-48_K8	Host phylogeny and fitness heterogeneity influencing persistence	Yes	Model-based inference; limited direct clinical validation
Kloos et al., 2021 [14]	Germany/Norway	Experimental evolution	Clinical E. coli isolates	IncR and IncC MDR plasmids	Niche-associated adaptation involving global regulatory changes	Yes	Laboratory evolution of clinical isolates

Ares-Arroyo et al., 2022 [31]	Spain	Multi-omic study	Haemophilus influenzae	ColE1-like pB1000	Metabolic and membrane remodeling supporting compensation	No	Limited to one bacterial plasmid system
Zhang et al., 2022 [16]	China	Experimental and in vivo study	E. coli K-12	RP4 MDR plasmid	Regulatory and transcriptional rewiring, enhancing adaptation and colonization	Yes	The murine model may not fully represent human microbiomes
Hall et al., 2021 [28]	United Kingdom	Experimental evolution and transcriptomics	Pseudomonas fluorescens	Large plasmids and chromosomal MGE	Conflict-specific compensation and suppression of maladaptive gene expression	Yes	Controlled laboratory system
DelaFuente et al., 2024 [32]	Spain	Mechanistic and modelling synthesis	Plasmid–bacteria associations relevant to AMR	AMR plasmids	Global epistasis may help explain predictable plasmid–host associations and persistence.	Indirect	Conceptual and model-supported; not a direct clinical study
Fernández-Calvet et al., 2023 [33]	Spain	Experimental study	Clinical Enterobacteriaceae	pOXA-48 plasmid	Variable plasmid fitness effects, including neutral or beneficial effects in native hosts	Indirect	Focused on one clinically important plasmid type
Rebelo et al., 2023 [34]	Portugal	Modelling and simulation study	Generic donor–recipient bacterial populations	Conjugative plasmids	Cost-driven persistence influenced by compensatory mutations and spatial structure	Yes	An in silico model is dependent on assumptions

3.2. Antibiotic- and stressor-associated mobilization pathways

Eight studies examined antibiotic- or stressor-associated mobilization of plasmids or closely related MGEs (Table 2) [6], [8], [9], [11], [17], [18], [35], [36]. Compared with the persistence domain, this evidence base was smaller and more heterogeneous. It included experimental studies, mechanistic syntheses, and narrative reviews. As a result, conclusions from this domain should be interpreted as mechanistically informative but less uniformly supported than findings from the persistence literature.

Two broad mobilization pathways were identified. The first involved SOS- or LexA-associated activation of MGEs in response to DNA damage or antibiotic-induced stress [8], [11], [18]. Experimental evidence provided direct support for this mechanism in specific systems, particularly where antibiotic exposure or plasmid entry was linked to MGE excision or transfer [11]. However, some supporting sources were review-based rather than primary experimental studies, which limits the strength of direct inference [8], [9], [18].

The second pathway involved SOS-independent or partially SOS-independent mobilization associated with metabolic, oxidative, redox-related, or antibiotic-specific regulatory effects [6], [17], [35]. This mechanism was reported less consistently and appeared to be more context-dependent. Therefore, it is best interpreted as a complementary pathway rather than a universally dominant mechanism of plasmid or MGE mobilization.

Several studies also suggested that prolonged or sub-inhibitory antimicrobial exposure may increase transposition, conjugation, or HGT through cumulative selection rather than acute stress activation alone [6], [18], [36]. This indicates that mobilization may occur through both short-term stress responses and longer-term adaptive processes. However, the timing, magnitude, and reproducibility of these effects varied substantially across experimental systems.

Ecological context further influenced interpretation. Host-associated bacterial systems generally provided clearer mechanistic links between stress responses and MGE activity [11], [17], [35], whereas environmental systems showed greater variability in the timing and magnitude of gene transfer responses [9], [36]. Direct comparison across studies was limited by differences in bacterial taxa, stressors, exposure duration, transfer assays, and outcome measures.

The idea of a defined "mobilization window" was supported by some experimental studies but was not consistently quantified across the evidence base [11], [36]. Therefore, although the concept is biologically plausible, it should be presented as an emerging hypothesis rather than an established general principle.

Overall, antibiotic- and stressor-associated mobilization appears to be a multi-pathway and context-dependent process. The available evidence supports roles for SOS-associated activation, SOS-independent stress responses, antibiotic-specific regulatory effects, and selection-driven increases in HGT. However, the small number of primary studies, reliance on review-based synthesis for some mechanisms, and variability across systems limit the generalizability of a single mobilization model.

Table 2: Antibiotic- and Stressor-Associated Mobilization Pathways

Study	Country/setting	Study type	Host/system	Stressor or exposure	Proposed trigger	Mobilization outcome	Strength of evidence
Fornelos et al., 2016 [8]	Multiple settings	Mechanistic review	Multiple bacterial systems	DNA damage and stress responses	LexA-regulated MGE activation	Conceptual support for enhanced MGE activation	Review-based; indirect evidence
Partridge et al., 2018 [9]	Global	Narrative review	Clinical and environmental bacteria	Multiple antibiotic contexts	Plasmids, integrons, transposons, and ICEs	Synthesis of ARG dissemination mechanisms	Review-based; broad but indirect
Pons et al., 2023 [11]	France	Experimental study	Salmonella enterica	Plasmid entry and associated stress	Transient SOS response	SGI1 excision and transfer	Strong experimental support in a defined system
Yao et al., 2022 [6]	China	Experimental study	Escherichia coli	Antibiotic selection pressure	Selection-driven transposition	Increased plasmid-borne ARG movement	Direct experimental support
Huang et al., 2022 [17]	China	Experimental study	E. coli, Salmonella, and Pseudomonas	Reductive stress	Metabolic or redox regulation	Increased plasmid transfer	Direct experimental support for redox-associated plasmid transfer

Liu et al., 2022 [18]	Denmark	Mini-review	Broad bacterial taxa	Multiple antimicrobial exposures	SOS response, membrane stress, metabolic perturbation, and antimicrobial-induced transfer mechanisms	Conceptual support for enhanced HGT	Review-based synthesis of antimicrobial-induced HGT mechanisms
Zhao et al., 2025 [35]	Denmark/China	Experimental study	E. coli carrying IncI1 and IncFII plasmids	Antibiotic exposure	Mechanistic divergence between SOS activation and antibiotic-induced plasmid conjugation	Antibiotic-induced conjugation may occur through mechanisms not fully explained by SOS activation.	Strong experimental support for a multi-pathway interpretation
Jutkina et al., 2018 [36]	Sweden	Experimental study	Environmental bacterial communities	Sub-MIC antibiotics and biocides	Stress- or selection-associated HGT	Increased gene transfer frequency	Experimental support in environmental systems

3.3. Clinical and translational evidence

Eleven studies contributed evidence on clinical and translational aspects of plasmid-mediated AMR (Table 3) [2–4], [19], [20], [23], [37–41]. Compared with the mechanistic evidence base, this domain was more heterogeneous and generally less mature. Studies included genomic surveillance, clinical reports, systematic review evidence on fecal microbiota transplantation (FMT), and preclinical anti-plasmid or resistance-suppression strategies.

Clinical genomic surveillance studies showed that plasmid-mediated AMR transmission in healthcare settings may be more complex than routine microbiological surveillance can detect [2–4]. Whole-genome sequencing and plasmid-resolved approaches provided evidence of intra-patient, inter-patient, and interspecies dissemination of resistance-associated plasmids, including carbapenemase-encoding plasmids. However, the strength of inference varied across studies. Some studies provided high-resolution genomic evidence, whereas others were limited by single-center designs, narrow patient populations, or a lack of direct intervention assessment.

FMT-related studies provided evidence for microbiome-based reduction of multidrug-resistant organism carriage, but outcomes varied by clinical context [19], [20], [37], [38]. FMT showed strong clinical effectiveness in recurrent Clostridioides difficile infection [19], but its effectiveness for AMR decolonization was more modest and inconsistent [20], [38]. This difference suggests that restoring microbiome structure does not necessarily translate into predictable removal of resistance reservoirs. Safety concerns were also reported, including donor-derived transmission of resistant organisms [37], indicating the need for rigorous donor screening and careful clinical monitoring.

Preclinical anti-plasmid strategies, including CRISPR-Cas-based plasmid targeting, plasmid-curing approaches, and RecA inhibition, showed promise in experimental systems [23], [39–41]. These approaches demonstrated the potential to reduce plasmid carriage, restore antibiotic susceptibility, generate plasmid-cured strains for host–plasmid studies, or delay resistance evolution under controlled conditions. However, they remain largely preclinical. Major barriers to translation include delivery, specificity, off-target effects, microbiome disruption, emergence of escape mutants, and lack of human clinical validation.

Across the translational evidence base, readiness for clinical application varied considerably. FMT is clinically established for recurrent C. difficile infection but remains investigational for AMR decolonization. Genomic surveillance is increasingly feasible but not yet routinely integrated into plasmid-level infection control in many settings. Anti-plasmid approaches remain experimental. No included study directly evaluated a plasmid-targeted intervention in a controlled human clinical trial.

Overall, the clinical and translational evidence suggests an evolving but incomplete field. Current findings support the relevance of plasmid-level surveillance and microbiome-informed interventions, but they also highlight important limitations, including small sample sizes, single-center designs, heterogeneity of outcomes, limited randomized trial evidence, and incomplete safety assessment.

Table 3: Clinical and Translational Evidence Mapping of Plasmid-Mediated AMR and Mitigation Strategies

Study	Country/setting	Study type	Focus	Main finding	Translational readiness	Key limitation
Sobkowiak et al., 2025 [4]	United Kingdom	Genomic surveillance	Hospital plasmid transmission surveillance	Identified potential and confirmed plasmid transmission events that were not fully captured by routine surveillance	Early translational use in infection control	Single-center; no interventional assessment
Ludden et al., 2021 [3]	United Kingdom	Prospective genomic cohort	E. coli and AMR gene transmission in hematology patients	Identified transmission clusters and highlighted the complexity of endogenous and nosocomial AMR sources	Observational translational evidence	ESBL-focused; colonization and infection overlap complicates inference
de Man et al., 2021 [2]	Japan	Multi-center genomic surveillance	Carbapenem-resistant Enterobacteriaceae	Identified plasmid-mediated dissemination of carbapenem resistance across species	Translational surveillance insight	Regional focus; no intervention tested
Hao et al., 2020 [23]	China	Proof-of-concept experimental study	CRISPR-Cas plasmid curing	Demonstrated plasmid curing and restored carbapenem susceptibility in clinical CRE isolates	Preclinical	Delivery systems not clinically optimized
Tavoukjian, 2019 [20]	United States	Systematic review and meta-analysis	FMT for MDR bacterial decolonization	Reported partial decolonization success, with variable outcomes across organisms	Early clinical evidence	Small and heterogeneous studies; limited randomized evidence
DeFilipp et al., 2019 [37]	United States	Case report	FMT safety	Reported donor-derived ESBL-producing E. coli transmission following FMT	Safety signal	Case report; not generalizable but clinically important
Kelly et al., 2016 [19]	Canada	Randomized controlled trial	FMT for recurrent C. difficile infection	Donor FMT showed high cure rates and restoration of microbial diversity	Established for recurrent CDI; indirect relevance to AMR	Not designed primarily for AMR decolonization
Manges et al., 2016 [38]	United States	Narrative review/case-based synthesis	FMT for MDR organism decolonization	Suggested possible decolonization of resistant organisms in selected cases	Early clinical hypothesis-generating evidence	No robust randomized evidence; durability unclear

Buckner et al., 2018 [39]	United Kingdom	Narrative review	Anti-plasmid strategies	Reviewed chemical curing, conjugation inhibition, phage-based approaches, and CRISPR strategies	Preclinical/conceptual	Limited human validation
Alam et al., 2016 [40]	United States	Experimental study	RecA inhibition	Showed enhanced antibiotic activity and delayed resistance evolution in experimental models	Preclinical	No human safety or efficacy data
Yen et al., 2024 [41]	United States	Experimental methods study	Cas9-based plasmid curing in Gram-negative bacteria	Developed a conjugative CRISPR-Cas9 system to cure common plasmids among Enterobacterales	Preclinical/methodological	Useful for plasmid-curing and host–plasmid studies, but not clinically validated

4. Discussion

This scoping review synthesized evidence on plasmid-mediated antimicrobial resistance (AMR) in the human microbiome across three interconnected domains: plasmid persistence, antibiotic- and stressor-associated mobilization, and clinical or translational implications. These domains describe related processes through which plasmids may be maintained, activated, and disseminated within microbial communities. However, the strength and maturity of evidence differed across domains, so the findings should be interpreted as a structured map of current evidence rather than proof of a single universal pathway of plasmid-mediated AMR dissemination.

A major finding was that plasmid persistence is supported by a comparatively strong mechanistic evidence base, mainly from experimental evolution, multi-omic, modelling, and clinical-isolate studies. Across these studies, host–plasmid co-adaptation and compensatory evolution were frequently reported as mechanisms that reduce the fitness burden of plasmid carriage and support longer-term plasmid maintenance. These adaptations included chromosomal mutations, plasmid rearrangements, regulatory changes, metabolic remodeling, and host–plasmid epistatic interactions [5], [10], [13–16], [25–34]. This evidence challenges the assumption that resistance plasmids are necessarily unstable once antibiotic selection is removed.

Nevertheless, this conclusion should be interpreted cautiously. Much of the evidence comes from controlled laboratory systems using a limited range of bacterial hosts, particularly Escherichia coli and Pseudomonas spp. Such systems are useful for identifying mechanisms but may not fully represent complex human microbiomes. In natural or clinical communities, plasmid persistence may also be shaped by host diversity, spatial structure, microbial density, interspecies interactions, immune pressures, and repeated antimicrobial exposure. Therefore, although compensatory evolution is well supported, its relative importance in human microbiomes remains uncertain.

The review also identified variability in the relative contributions of host-driven and plasmid-driven adaptation. Experimental evolution studies generally emphasized host genomic compensation, whereas modelling, microbiome-associated studies, and recent work on global epistasis suggest that plasmid evolution, host phylogeny, plasmid–host compatibility, and ecological structure may also influence persistence [15], [32–34]. This indicates that plasmid persistence is unlikely to result from a single mechanism. Instead, it may reflect the combined effects of host adaptation, plasmid stability systems, recurrent horizontal transfer, and ecological conditions that favour plasmid maintenance.

Evidence on antibiotic- and stressor-associated mobilization was more heterogeneous. Several studies supported the role of antibiotic exposure in activating mobile genetic elements (MGEs), particularly through SOS- or LexA-associated responses to DNA damage [8], [11], [18]. However, not all mobilization appears to follow this pathway. Experimental and review-based evidence suggests that metabolic, oxidative, redox-related, and antibiotic-specific regulatory effects may also influence plasmid transfer or MGE activation through mechanisms partly independent of the classical SOS response [6], [17], [35]. This supports the interpretation of mobilization as a multi-pathway and context-dependent process rather than a single uniform response.

Timing and ecological context remain unresolved. Some experimental studies support the possibility that antibiotic or stress exposure creates a temporary period of increased genetic exchange, but the existence, duration, and clinical relevance of this "mobilization window" have not been consistently quantified [11], [36]. Similarly, transfer dynamics vary across host-associated, environmental, laboratory, and clinical systems. Differences in bacterial taxa, stressors, exposure duration, microbial density, and transfer assays limit direct comparison across studies.

The clinical and translational evidence was less mature than the mechanistic evidence. Genomic surveillance studies suggest that plasmid-mediated AMR transmission in healthcare settings can be more complex than routine microbiological surveillance detects [2–4]. Whole-genome sequencing and plasmid-resolved approaches can identify intra-patient, inter-patient, and interspecies dissemination of resistance-associated plasmids. However, many studies remain limited by single-center designs, selected patient populations, short observation periods, and incomplete linkage between plasmid transmission and clinical outcomes.

Interventional evidence remains particularly limited. Fecal microbiota transplantation (FMT) is clinically established for recurrent Clostridioides difficile infection, but its role in AMR decolonization is less certain [19], [20], [38]. Available evidence suggests possible reductions in multidrug-resistant organism carriage in selected contexts, but outcomes are variable, and safety concerns remain, including donor-derived transmission of resistant organisms [37]. Similarly, CRISPR-Cas-based plasmid targeting, plasmid-curing approaches, and RecA inhibition show promise in experimental models but remain preclinical because of challenges related to delivery, specificity, safety, microbiome disruption, and potential escape mutants [23], [39–41].

Taken together, these findings show a clear translational gap. Mechanistic studies have advanced understanding of plasmid persistence and mobilization, but clinical strategies that directly target plasmid dynamics remain underdeveloped. No included study evaluated a plasmid-targeted intervention in a controlled human clinical trial. This gap is important because successful translation will require not only biological efficacy but also safe delivery, ecological stability, regulatory feasibility, and measurable clinical benefit.

Several limitations in the evidence base should be emphasized. First, the included studies were heterogeneous in design, biological system, measurement method, and scale of inference, limiting direct comparison across findings. Second, the geographical distribution of studies was skewed toward high-income settings, reducing generalizability to low- and middle-income countries. Third, many studies relied on laboratory systems or selected clinical cohorts, which may not capture the diversity of real-world commensal microbiomes. Finally, plasmid-mediated transmission remains difficult to detect because plasmids may move between bacterial hosts without clear clonal spread of the host organism. Short-read sequencing and culture-based approaches may therefore underestimate plasmid dynamics in clinical and natural microbiomes.

Importantly, this review does not support a deterministic model in which plasmids alone explain AMR emergence or dissemination. Rather, the evidence indicates that plasmid-mediated AMR is context-dependent and shaped by interactions between molecular mechanisms,

microbial ecology, antibiotic exposure, host factors, and healthcare environments. Plasmids and other MGEs are important contributors to AMR dynamics, but their relative influence varies across organisms, settings, and selective conditions.

Overall, the findings support integrating plasmid and mobilome perspectives into AMR research, surveillance, and intervention development. Future research should prioritize longitudinal multicenter studies, standardized HGT detection methods, improved plasmid-resolved sequencing, broader sampling of commensal microbiomes, and carefully designed clinical trials of microbiome-informed or plasmid-targeted interventions. These steps are needed to translate mechanistic insights into safe and effective strategies for reducing AMR transmission in real-world settings.

5. Conceptual Framework

The conceptual framework presented in Fig. 4 illustrates a context-dependent pathway linking antibiotic exposure, bacterial stress responses, plasmid mobilization, plasmid persistence, and antimicrobial resistance (AMR) dissemination within the human microbiome. The framework is not intended to suggest a fixed or deterministic sequence. Rather, it synthesizes evidence from molecular, ecological, and clinical studies to show how environmental pressures, mobile genetic element (MGE) activation, host–plasmid interactions, and clinical factors may interact to shape plasmid-mediated AMR dynamics.

The first stage of the framework is antibiotic exposure and environmental stress. Antibiotic exposure may occur at therapeutic or sub-inhibitory concentrations, while non-antibiotic stressors may include oxidative stress, inflammation, nutrient limitation, hospitalization, and environmental perturbations. These pressures operate within host and microbiome contexts shaped by immune status, medication use, microbiota composition, microbial density, and spatial structure. Together, these conditions may disturb microbial community balance and create selective environments that favour resistant bacteria or resistance-associated plasmids.

The second stage is stress-response activation and MGE activation. In response to antibiotic or environmental stress, bacterial cells may activate stress-response pathways such as the SOS response, which involves RecA activation and LexA cleavage following DNA damage. Other pathways, including redox and metabolic stress responses, membrane-associated responses, quorum sensing, and intercellular signaling, may also contribute under specific conditions. These responses can increase MGE activity by promoting plasmid excision, integron activation, transposon mobilization, and induction of conjugation-related genes. This stage represents the transition from environmental stress to increased genetic mobility.

The third stage is plasmid mobilization and horizontal gene transfer. Once MGEs are activated, antimicrobial resistance genes (ARGs) may move between bacterial cells through conjugation, transformation, or transduction. Transfer efficiency is influenced by plasmid-related factors, including conjugative machinery, host range, copy number, and stability systems. It is also shaped by host and environmental conditions, such as host compatibility, fitness cost, biofilm formation, microbial density, and spatial proximity. Through these mechanisms, ARGs may move between commensal bacteria and potentially pathogenic organisms.

The fourth stage is plasmid persistence in the microbiome. After transfer, plasmids may persist through both vertical and horizontal maintenance mechanisms. Vertical persistence may be supported by host–plasmid co-adaptation, compensatory evolution, regulatory rewiring, epistatic interactions, and plasmid stability systems such as toxin–antitoxin and partitioning systems. Horizontal maintenance may occur through ongoing low-level transfer within microbial communities. These mechanisms may allow plasmids and their associated ARGs to remain in commensal reservoirs even when continuous antibiotic selection is absent.

The fifth stage is AMR dissemination and clinical impact. The combined effects of plasmid mobilization and persistence may contribute to AMR spread within and beyond the host. Dissemination may occur through within-host transfer, between-host transmission, healthcare-associated spread, environmental pathways, and wider community circulation. Clinically, these processes may contribute to colonization with multidrug-resistant organisms, reduced treatment options, and increased healthcare burden.

The framework also highlights feedback loops and ecological interactions. Microbiome disruption may create new transfer opportunities, while plasmid carriage may impose fitness costs that drive compensatory adaptation. Continued environmental or antibiotic pressure may select for resistant bacterial hosts and plasmids, and clinical interventions may reshape selective pressures and transmission dynamics. These feedback loops indicate that plasmid-mediated AMR is not purely linear but is influenced by repeated interactions between microbial ecology, host conditions, treatment practices, and healthcare environments.

Finally, the framework identifies potential intervention points across the pathway. These include reducing antibiotic exposure through antimicrobial stewardship, blocking stress-response pathways such as SOS/LexA/RecA signaling, inhibiting plasmid mobilization through conjugation inhibitors or anti-plasmid strategies, reducing plasmid persistence through plasmid-curing approaches or stability-system targeting, and limiting dissemination through plasmid-resolved surveillance, infection control, and microbiome restoration. Together, these intervention points provide a structured basis for future research, surveillance, and translational strategies aimed at reducing plasmid-mediated AMR transmission.

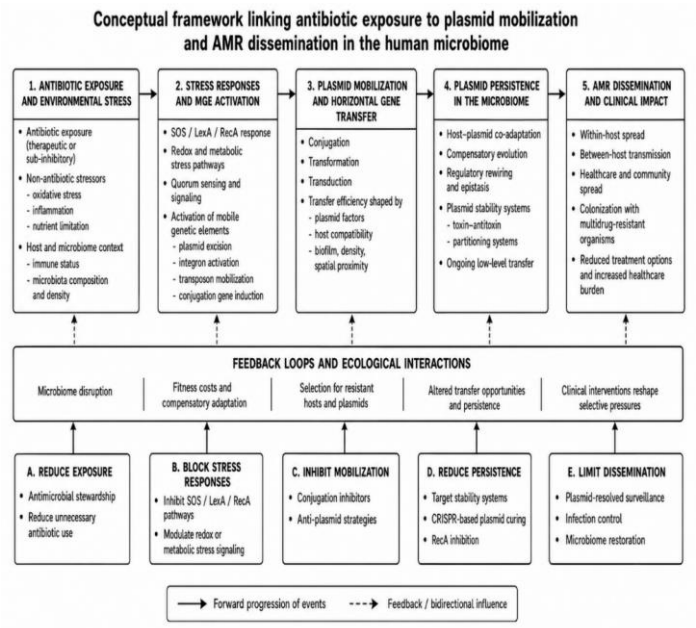

Fig. 4: Conceptual Framework Linking Antibiotic Exposure, Stress-Response Activation, Plasmid Mobilization, Plasmid Persistence, and Antimicrobial Resistance Dissemination in the Human Microbiome.

6. Insights and Implications

This review identifies three interrelated themes in plasmid-mediated antimicrobial resistance (AMR) within the human microbiome: plasmid persistence through host–plasmid co-adaptation and compensatory evolution, stress-associated mobilization of mobile genetic elements, and the role of commensal microbial communities as potential reservoirs of transferable resistance genes [5], [10], [13–18], [25–36]. Together, these themes suggest that plasmid-mediated AMR is a dynamic and context-dependent process shaped by interactions among molecular mechanisms, microbial ecology, antibiotic exposure, and clinical environments [2–6], [15], [16].

The strongest evidence relates to plasmid persistence. Mechanistic and experimental studies show that plasmid carriage can be stabilized through adaptive processes, including compensatory mutations, regulatory remodeling, host–plasmid co-adaptation, and plasmid stability mechanisms [10], [13–16], [25–34]. Evidence also supports the role of antibiotic and environmental stress in promoting MGE mobilization, particularly through SOS-dependent pathways, although redox, metabolic, and other stress-response mechanisms may contribute under specific conditions [6], [8], [11], [17], [18], [35], [36]. These findings provide a biological basis for understanding how resistance genes may persist within microbial communities and move across bacterial populations.

However, several aspects remain uncertain. The evidence base is still dominated by laboratory-based studies, with fewer in vivo, longitudinal, and clinical investigations [10], [13–18], [25–36]. As a result, the frequency, timing, and clinical relevance of plasmid-mediated transfer in natural human microbiomes remain incompletely defined [2–4], [15], [16]. The relative importance of different mobilization pathways also appears to vary across bacterial species, plasmid types, stressors, and ecological settings [6], [11], [17], [18], [35], [36]. Therefore, findings from controlled experimental systems should not be assumed to apply uniformly to complex clinical or community microbiomes.

The translational implications are important but still emerging. CRISPR-based plasmid targeting, RecA inhibition, conjugation blockade, and fecal microbiota transplantation show potential for reducing resistance reservoirs or interrupting plasmid-mediated AMR dynamics [19], [20], [23], [37–41]. Nevertheless, these strategies require further validation because of unresolved challenges related to delivery, specificity, safety, ecological disruption, and long-term effectiveness [20], [37–41]. At present, they should be interpreted as promising but not yet broadly established interventions for AMR control.

From a public health and clinical perspective, the findings support greater integration of plasmid-level and mobilome-aware approaches into AMR surveillance [2–4]. This includes wider use of plasmid-resolved genomic tools, long-read sequencing, longitudinal sampling, and standardized methods for detecting horizontal gene transfer in complex microbial communities [2–4], [15], [16]. Strengthening antimicrobial stewardship also remains essential, as reducing unnecessary antibiotic exposure may limit both selective pressure and stress-associated mobilization [1], [6], [11], [17], [18], [35], [36]. Infection prevention strategies may further benefit from considering commensal microbiota as possible reservoirs of resistance, rather than focusing exclusively on cultured clinical pathogens [2–4], [7].

Overall, plasmid-mediated processes represent an important but context-dependent component of AMR dynamics [5], [10], [13–18], [25–36]. Future research should prioritize multicenter longitudinal studies, broader sampling from underrepresented regions, improved plasmid-resolved bioinformatics, and carefully designed clinical trials of microbiome-informed or plasmid-targeted interventions [2–4], [19], [20], [23], [37–41]. Strengthening evidence across molecular, ecological, and clinical domains will be essential for translating current mechanistic insights into effective and sustainable AMR mitigation strategies.

7. Conclusion

This scoping review shows that plasmid-mediated antimicrobial resistance (AMR) in the human microbiome is a context-dependent process shaped by plasmid persistence, stress-associated mobilization, microbial ecology, and clinical selective pressures. Across the included studies, plasmid persistence was commonly linked to host–plasmid co-adaptation, compensatory evolution, regulatory flexibility, and plasmid stability mechanisms, while antibiotic and environmental stressors may promote horizontal gene transfer through SOS-dependent and alternative stress-response pathways. However, the evidence remains heterogeneous, with most mechanistic insights derived from laboratory-based studies and limited longitudinal, in vivo, and multicenter clinical validation. Although genomic evidence suggests that plasmid-

mediated transmission may be underdetected by conventional surveillance, its population-level impact and clinical burden remain incompletely defined. Emerging interventions, including fecal microbiota transplantation, CRISPR-based plasmid targeting, conjugation inhibition, and RecA-related approaches, show promise but require rigorous validation for safety, delivery, specificity, ecological impact, and long-term effectiveness. Overall, AMR should not be viewed solely as a pathogen-centred problem but also as a process shaped by plasmid dynamics and microbiome-level interactions, underscoring the need for plasmid-resolved surveillance, standardized HGT detection methods, longitudinal clinical studies, and carefully designed translational research.

8. Declarations

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Author Contributions

Conceptualization and methodology: QBO, TAH.
Literature search, screening, and data extraction: QBO, TAH.
Data synthesis and interpretation: QBO, OJA, GSA, MAI, SHA, GNA.
Manuscript drafting and revision: QBO, ZMA, MKT, WGI, MAE.
Supervision and final approval: QBO, TAH, OJA, GSA, MAI, SHA.

Competing Interests

The authors declare that they have no known competing financial or non-financial interests that could have influenced the work reported in this manuscript.

Ethics Approval

Not applicable. This study is a scoping review based exclusively on previously published literature. No human participants, animals, or identifiable personal data were involved.

Consent to Participate

Not applicable.

Consent to Publish

Not applicable.

Data Availability

No new data were generated or analyzed in this study. All information synthesized in this review was derived from previously published sources cited in the reference list.

Code Availability

Not applicable. No code was generated or used for this review.

Clinical Trial Registration

Not applicable. This study was not a clinical trial.

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