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Review Article

Biotherapy Strategies for Modulating the Gut Microbiome to Prevent and Treat Infectious Diseases

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Abstract

The gut microbiome plays a central role in maintaining intestinal homeostasis, regulating host immunity, and providing colonization resistance against invading pathogens. Disruption of this microbial ecosystem can facilitate pathogen colonization, antimicrobial resistance, impaired barrier function, and increased susceptibility to infectious diseases. Consequently, therapeutic strategies that restore or selectively modify the gut microbiome have emerged as promising complements to conventional antimicrobial approaches. This narrative review examines current biotherapy strategies for modulating the gut microbiome to prevent and treat infectious diseases, with emphasis on their mechanisms, therapeutic applications, clinical evidence, and translational challenges. Major approaches include probiotics, prebiotics and synbiotics, fecal microbiota transplantation, live biotherapeutic products, defined microbial consortia, and postbiotics or microbiome-derived metabolites. These interventions may enhance colonization resistance through competitive exclusion of pathogens, production of antimicrobial metabolites, restoration of microbial diversity, reinforcement of intestinal barrier integrity, and modulation of host immune responses. Their applications are particularly established in Clostridioides difficile infection, while emerging evidence supports potential benefits against multidrug-resistant bacterial colonization, enteric infections, and selected viral, fungal, and parasitic diseases. Despite promising therapeutic outcomes, variability in microbiome composition, treatment response, safety, formulation, manufacturing, and regulatory requirements continues to limit widespread clinical implementation. Advances in precision microbiome profiling, engineered microbial therapeutics, and personalized interventions may improve efficacy and therapeutic predictability. Overall, microbiome-targeted biotherapies represent an evolving strategy for infection prevention and treatment, with substantial potential to complement antimicrobial therapy and contribute to more sustainable approaches to infectious-disease management.

Keywords: Gut microbiome, biotherapy, probiotics, fecal microbiota transplantation, infectious diseases and microbiome modulation

Introduction

The gut microbiome is a complex and dynamic microbial ecosystem that plays a fundamental role in intestinal homeostasis, epithelial integrity, metabolism, and immune regulation. One of its most important functions is colonization resistance, through which resident microorganisms protect the host against invading pathogens by competing for nutrients and ecological niches, producing inhibitory metabolites and antimicrobial compounds, and interacting with host defense

mechanisms (Buffie and Pamer, 2013; Abah *et al.,* 2025). Colonization resistance is not determined solely by microbial diversity or the abundance of individual taxa but reflects interactions among microbial communities, host physiology, environmental exposures, and metabolic processes (Woelfel *et al.,* 2024). These protective functions position the gut microbiome as an important component of the host's defense against infectious diseases and provide a biological rationale for therapeutic approaches that seek to preserve or restore microbiome-mediated protection.

Disruption of the gut microbial ecosystem, or dysbiosis, can weaken these protective functions and create ecological conditions favorable to pathogen colonization and expansion. Antibiotic exposure is a major driver of such disruption, as antimicrobial treatment can eliminate protective microorganisms, alter microbial metabolic activity, and reduce resistance to opportunistic and antimicrobial-resistant pathogens (Pamer, 2016). The consequences are particularly evident in Clostridioides difficile infection, in which disruption of the intestinal microbiota facilitates pathogen proliferation and recurrent disease. Loss of microbiome-mediated resistance may also promote intestinal colonization by multidrug-resistant organisms, highlighting the microbiome as an important determinant of infection risk and antimicrobial resistance. Contemporary evidence indicates that colonization resistance involves interconnected microbial, host, environmental, and metabolic determinants, suggesting that effective infection management may require restoration of ecological functions in addition to direct pathogen elimination (Woelfel *et al.,* 2024).

Recognition of these relationships has driven the development of biotherapy strategies designed to modify, restore, or supplement the gut microbiome. Conventional approaches, including probiotics, prebiotics, and synbiotics, aim to support beneficial microbial populations and influence pathogen exclusion, intestinal barrier function, microbial metabolism, and host immunity. More direct restoration approaches include fecal microbiota transplantation (FMT), defined microbial communities, and live biotherapeutic products (LBPs), which seek to re-establish protective microbiome functions following ecological disruption (Kim *et al.*, 2024). FMT has demonstrated substantial therapeutic value in recurrent *C. difficile* infection, while the development of standardized microbiota-based products represents an important transition toward more controlled and reproducible microbiome therapeutics (Hunt *et al.,* 2024; Pettit *et al.,* 2024). These developments have strengthened the clinical rationale for microbiome modulation as a component of infectious-disease prevention and treatment.

The field is increasingly progressing from broad microbiota replacement toward standardized, defined, and functionally targeted biotherapies. LBPs represent an important advance because they can provide selected microbial communities or functions while potentially reducing some of the variability associated with conventional donor-derived interventions (Kim *et al.,* 2024; Sehgal and Feuerstadt, 2024). Recent clinical and translational developments have particularly established microbiome-based therapies as an important strategy for preventing recurrent C. difficile infection, although their application to other infectious diseases remains under active investigation (Hunt *et al.*, 2024; Lucky *et al.*, 2025). In parallel, engineered probiotics are being explored as programmable therapeutic platforms capable of delivering antimicrobial, immunomodulatory, or other targeted functions within the gastrointestinal tract (Meng *et al.,* 2024; Moses *et al.,* 2026). Despite these advances, variability in microbiome composition and treatment response, safety considerations, manufacturing requirements, standardization, and regulatory challenges continue to influence clinical translation (Pettit *et al.,* 2024; Lucky *et al.,* 2025).

This narrative review examined biotherapy strategies for modulating the gut microbiome to prevent and treat infectious diseases. It focuses on approaches that restore, support, or deliberately reshape the intestinal microbial ecosystem to strengthen resistance against pathogenic organisms and improve infection outcomes. The review first considers the contribution of the gut microbiome to infectious-disease susceptibility, emphasizing colonization resistance, dysbiosis, microbial interactions, intestinal barrier function, and host immune regulation. It then examines major biotherapeutic approaches, including probiotics, prebiotics and synbiotics, fecal microbiota transplantation, live biotherapeutic products, defined microbial consortia, and microbiome-derived or postbiotic interventions. Particular attention is given to the mechanisms through which these strategies influence pathogen exclusion, microbial competition, metabolite production, epithelial protection, and host immune responses. Their applications are subsequently considered across clinically relevant infectious diseases, with emphasis on recurrent Clostridioides difficile infection, enteric bacterial infections, multidrug-resistant bacterial colonization and infection, and emerging applications involving viral, fungal, and parasitic infections. The review further considers clinical evidence, therapeutic effectiveness, safety, limitations, and barriers to translation into routine clinical practice. Emerging precision, engineered, and personalized approaches are also discussed in relation to their potential to complement conventional antimicrobial therapy. By integrating biological mechanisms with therapeutic and translational evidence, this review aims to provide a focused assessment of the current role of microbiome-modulating biotherapies and highlight priorities for their safe, effective, and clinically relevant development in infectious-disease prevention and treatment.

Gut Microbiome in Infectious Disease

The gut microbiome is a major determinant of susceptibility to infectious disease because its ecological organization and functional activity influence the ability of microorganisms to establish, persist, and expand within the gastrointestinal tract. Its protective capacity depends on interactions among resident microbial communities, the intestinal environment, and host

physiology rather than on microbial diversity alone (Caballero-Flores *et al.,* 2023; Woelfel *et al.,* 2024). These interactions create an ecological environment that can restrict invading organisms while supporting physiological stability. Conversely, disturbances in microbial composition or function can alter this balance and increase opportunities for pathogen establishment. The gut microbiome should therefore be considered an active component of host defense, with its ecological state helping to determine the outcome following exposure to infectious organisms (Fang *et al.*, 2024).

Microbiome-Mediated Colonization Resistance

Colonization resistance describes the capacity of resident gut microorganisms to prevent or limit the establishment and expansion of invading pathogens. It represents a collective ecological property generated by microbial competition, community interactions, metabolic activity, and communication with the host (Caballero-Flores *et al.,* 2023). Competition for nutrients and intestinal niches can restrict resources available to invading organisms, while microbial metabolism can modify the intestinal environment and influence pathogen fitness (Jones *et al.,* 2025). The metabolic activities of commensal microorganisms are particularly important because they determine the availability and transformation of substrates that can either restrict or support pathogen growth. In Salmonella infection, for example, an intact microbiota contributes to resistance against intestinal invasion by creating ecological conditions unfavorable to pathogen expansion (Deng and Wang, 2024). Colonization resistance is consequently dynamic and context dependent, varying with microbial community structure, nutrient availability, host physiology, and environmental exposures (Woelfel *et al.,* 2024). This explains why apparently modest changes in microbial function can sometimes produce substantial differences in susceptibility to infection.

Table 1. Principal gut microbiome determinants of resistance to infectious pathogens

Microbiome determinant	Roles in infection resistance	Effect of disruption	Reference
Community structure	Maintains ecological competition and limits pathogen establishment	Loss of ecological stability and increased colonization	Caballero-Flores et al. (2023); Woelfel et al. (2024)
Nutrient availability	Limits access of invading pathogens to essential growth substrates	Greater resource availability for pathogen expansion	Deng and Wang (2024); Jones et al. (2025)
Microbial metabolism	Shapes the intestinal environment and influences pathogen fitness	Creation of pathogen-permissive metabolic ninche	Woelfel et al. (2024); Jones et al. (2025)
Microbiome–host interaction	Supports intestinal homeostasis and coordinated host defense	Impaired host–microbe balance and increased susceptibility	Fang et al. (2024); Wang et al. (2025)
Ecological stability	Preserves functional colonization resistance	Increased susceptibility to opportunistic and resistant organisms	Pamer (2016); Grießhammer et al. (2025); Yang et al. (2025)

Dysbiosis and Pathogen Colonization

Dysbiosis can compromise the ecological stability required for effective colonization resistance and thereby increase the likelihood of pathogen establishment. Antibiotic treatment remains one of the most important causes because it can substantially alter microbial communities and remove organisms that normally constrain opportunistic and

antimicrobial-resistant bacteria (Pamer, 2016). However, microbiome disruption is not restricted to antibiotics. Diet, disease, inflammation, hospitalization, and non-antibiotic medications can also modify microbial ecology and influence susceptibility to infection (Woelfel *et al.,* 2024). Recent evidence demonstrates that non-antibiotic drugs can disrupt colonization resistance against enteropathogens, emphasizing the broader influence of medication-associated microbiome alterations (Grießhammer *et al.,* 2025). Dysbiotic environments may also alter nutrient availability and microbial metabolic interactions in ways that favor pathogen expansion (Jones *et al.*, 2025). This relationship extends to antimicrobial-resistant organisms: microbiome characteristics have been associated with resistance to colonization by carbapenem-resistant Klebsiella pneumoniae among intensive-care patients (Yang *et al.,* 2025). Dysbiosis is therefore better understood as an ecological state that can facilitate pathogen colonization rather than simply as a reduction in microbial diversity.

Gut Microbiome–Host Immune Interactions

The gut microbiome is closely integrated with the host immune system and contributes to the maintenance of mucosal homeostasis and antimicrobial defense. Resident microorganisms continuously interact with intestinal epithelial and immune cells, while host immune mechanisms influence microbial distribution and community stability (Wang *et al.,* 2025). Microbial signals and metabolites participate in this bidirectional communication and help regulate local immune activity and intestinal inflammatory responses (Fang *et al.,* 2024). During infection, this relationship becomes particularly dynamic because immune activation can modify the microbial environment, while microbiome composition and activity can influence the magnitude and resolution of inflammation (McGowen *et al.,* 2025). Dysbiosis may consequently disturb immune homeostasis and weaken coordinated host responses, creating conditions that favor persistence or expansion of opportunistic organisms (Tewari and Dey, 2024). The microbiome–immune axis therefore represents an important determinant of infectious-disease susceptibility and provides a biological foundation for interventions aimed at restoring microbial and host homeostasis.

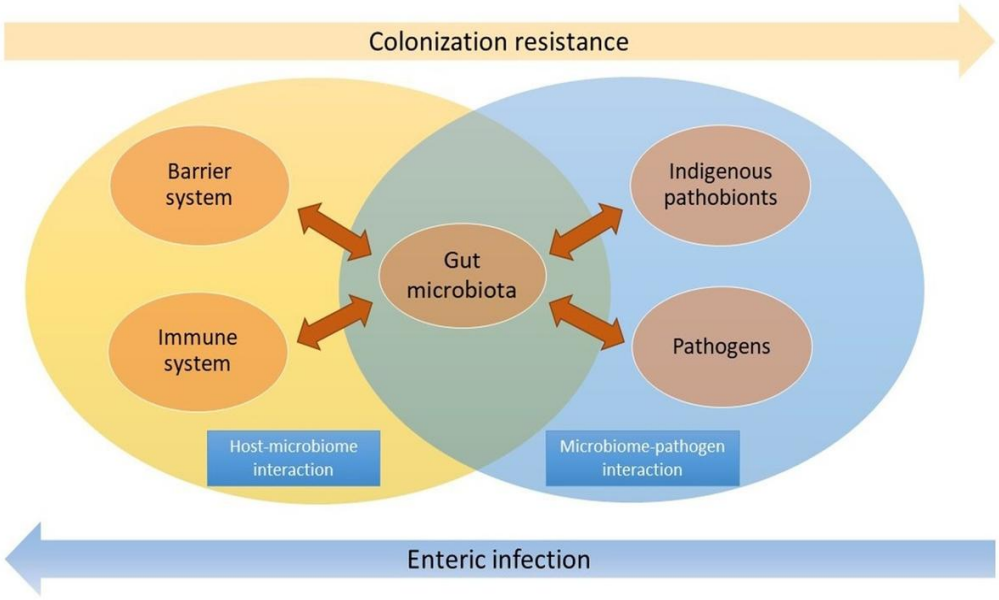


Figure 1. Gut microbiome–host–pathogen interactions determining susceptibility to infectious disease. The gut microbiome interacts dynamically with the intestinal barrier and host immune system while contributing to resistance against pathogen colonization. Disruption of these interactions can impair microbiome-mediated protection and increase susceptibility to infectious disease.
Source: Chen *et al.* **(2024)**

Biotherapy Strategies for Modulating the Gut Microbiome

Biotherapy strategies for modulating the gut microbiome encompass interventions designed to introduce beneficial microorganisms, support endogenous microbial communities, restore disrupted microbial ecosystems, deliver defined microbial consortia, or provide microbiome-derived functional products. Within infectious diseases, these approaches aim primarily to enhance colonization resistance, restore microbial homeostasis, and modulate pathogen-associated microbial functions. The major strategies considered in this section are probiotics, prebiotics and synbiotics, fecal microbiota transplantation (FMT), live biotherapeutic products and defined microbial consortia, and postbiotics and microbiome-derived metabolites (Pribyl *et al.*, 2025).

Probiotics

Probiotics are live microorganisms administered in adequate amounts to provide a health benefit and remain among the most extensively studied microbiome-directed interventions. Their potential in infectious diseases is based on their ability to influence the intestinal microbial environment and support host–microbiome homeostasis. Importantly, probiotic activity is highly strain-, dose-, formulation-, and disease-specific; consequently, evidence supporting one preparation cannot automatically be generalized to other probiotic products. A systematic review and meta-analysis of probiotic use as an adjunct in infectious diseases found potential benefits across several clinical infections, although considerable heterogeneity among strains, populations, and outcomes limits broad therapeutic conclusions (Nelwan *et al.,* 2024; Abah *et al.,* 2025). Recent evidence further emphasizes that probiotic administration does not necessarily produce permanent colonization or substantial restructuring of the recipient microbiome. Instead, clinical effects may result from transient ecological or functional interactions with the existing microbial community. This distinction is important when considering probiotics as preventive or therapeutic agents because microbiome modulation should not be equated with microbiome replacement. Evidence from recent randomized

trials and meta-analyses indicates that probiotics can influence microbial composition and selected functional outcomes, but responses vary considerably according to host characteristics and baseline microbiome configuration (Zhuang *et al.,* 2025). Thus, probiotics are best regarded as strain-specific microbiome modulators, with their infectious-disease applications requiring indication-specific clinical validation.

Prebiotics and Synbiotics

Prebiotics are substrates selectively utilized by host microorganisms that confer a health benefit, whereas synbiotics combine live microorganisms with substrates intended to provide complementary or synergistic effects. Unlike probiotics, these interventions primarily seek to modify the activity or composition of the existing microbial community rather than directly introduce a large external microbial population. Their relevance to infectious disease therefore lies in their capacity to support ecological functions associated with microbiome stability and favorable microbial metabolism. Recent clinical evidence indicates that prebiotics, probiotics, and synbiotics can modify selected components of the gut microbial community, although effects differ according to intervention type and host characteristics. In a 2025 meta-analysis of randomized trials in older adults, prebiotic and probiotic supplementation increased Bifidobacterium, while synbiotics influenced selected Bifidobacterium and Lactobacillus species and altered specific short-chain fatty acids (Abah *et al.,* 2025; Zhuang *et al.,* 2025). Similarly, a systematic review and meta-analysis involving 90 randomized controlled trials found that synbiotics produced more consistent improvements in several inflammatory biomarkers than prebiotics alone, although the certainty of evidence varied across outcomes (Zhang *et al.,* 2025). These findings suggest that prebiotics and synbiotics may provide a less invasive means of supporting endogenous microbiome functions. However, their effects remain dependent on substrate composition, dosage, duration, and the metabolic capacity of the recipient microbiota. Their role in infectious disease is therefore promising but remains less clinically established than microbiota-restoration approaches for recurrent Clostridioides difficile infection.

Fecal Microbiota Transplantation

FMT involves transferring processed fecal microbiota from a screened donor to a recipient to restore microbial functions disrupted by disease or antimicrobial exposure. It represents one of the most direct approaches to microbiome restoration and has its strongest clinical evidence in recurrent C. difficile infection, in which repeated antibiotic exposure can perpetuate microbiome disruption and predispose patients to recurrence. Recent clinical evidence continues to demonstrate substantial efficacy of FMT in recurrent infection, while emphasizing the importance of donor screening, treatment preparation, administration route, and recipient selection (Elendu *et al.,* 2025). Despite its therapeutic effectiveness, conventional FMT has inherent limitations. The microbial composition of donor material is complex and variable, and the contribution of individual organisms or microbial functions to clinical response is often difficult to determine. Concerns regarding pathogen transmission, donor variability, reproducibility, manufacturing, and long-term safety have consequently encouraged the development of more standardized microbiota-derived products (Pribyl *et al.,* 2025). The field is therefore progressively moving from conventional donor-derived transplantation toward defined and manufactured microbiome therapeutics. FMT remains an important proof of concept demonstrating that restoration of a disrupted microbial ecosystem can produce clinically meaningful protection against recurrent infection, while newer approaches seek to reproduce this effect with greater precision and consistency.

Live Biotherapeutic Products and Defined Microbial Consortia

Live biotherapeutic products (LBPs) represent a more standardized class of microbiome therapeutics consisting of characterized live microorganisms intended to prevent, treat, or cure disease. Their development addresses several limitations of conventional FMT by permitting greater control over microbial composition, manufacturing, quality assurance, dosing, and administration. The increasing clinical development of LBPs reflects the transition of microbiome science from experimental transplantation toward regulated therapeutic products (Tseng *et al.*, 2025). An important component of this transition is the development of defined microbial consortia, in which selected microorganisms are combined according to their complementary ecological or functional properties. Such products seek to reproduce specific protective functions without requiring the administration of an entire donor microbiome. Recent clinical and translational developments demonstrate the feasibility of single-strain, composite, and defined microbial products, particularly for recurrent C. difficile infection and restoration of colonization resistance (Tseng *et al.,* 2025). Broader advances in microbiome-derived therapeutics further indicate a movement toward rationally designed microbial communities with defined composition and predictable functional characteristics (Pribyl *et al.*, 2025). The major advantage of LBPs and defined consortia is therefore the possibility of converting microbiome restoration into a more reproducible therapeutic platform. Nevertheless, successful development requires reliable manufacturing, genetic and phenotypic characterization, appropriate dosing, assessment of colonization and persistence, and rigorous evaluation of safety. Host-specific differences in microbiome composition may also influence whether an administered microbial community successfully establishes its intended function. These considerations position defined microbial therapeutics as an important bridge between broad microbiome restoration and precision microbiome medicine.

Postbiotics and Microbiome-Derived Metabolites

Postbiotics provide an alternative strategy in which inanimate microorganisms, their components, or microbial-derived preparations are used to produce biological effects without administering viable microorganisms. This approach may offer advantages in stability, storage, formulation, and manufacturing while reducing some risks associated with the administration of live organisms (Amobonye *et al.,* 2025). Microbiome-derived metabolites represent a related but broader strategy in which specific products of microbial metabolism are targeted or administered to reproduce selected functions of a healthy microbiome. Microbial metabolites and structural components can influence the intestinal environment and host physiology, providing a potential means of delivering specific microbiome functions without reconstructing the entire microbial community. Recent literature has therefore increasingly examined postbiotics as functional alternatives or complements to live microbial interventions (Amobonye *et al.*, 2025). However, unlike FMT and certain LBPs, many postbiotic and metabolite-based applications for infectious diseases remain at preclinical or early translational stages. Their therapeutic development will require clearer identification of active components, dose–response relationships, pharmacological properties, and clinically relevant infectious-disease outcomes. Overall, these approaches represent a continuum from microbiome support to microbiome replacement and, increasingly, targeted delivery of microbial functions.

Table 2. Comparative characteristics of gut microbiome-targeted biotherapies

Biotherapy	Principal strategy	Reference
Probiotics	Introduce selected live microorganisms to modulate the existing gut microbial environment	Nelwan et al. (2024); Zhuang et al. (2025)
Prebiotics and synbiotics	Support beneficial endogenous microbial functions or combine microorganisms with selective substrates	Zhang et al. (2025); Zhuang et al. (2025)
Fecal microbiota transplantation (FMT)	Restore a disrupted microbial ecosystem using a screened donor-derived microbiome	Elendu et al. (2025); Pribyl et al. (2025)
Live biotherapeutic products and defined microbial consortia	Deliver characterized and standardized live microorganisms or selected microbial communities	Pribyl et al. (2025); Tseng et al. (2025)
Postbiotics and microbiome-derived metabolites	Deliver non-viable microbial components or specific microbial-derived functions	Amobonye et al. (2025); Pribyl et al. (2025)

Mechanisms of Biotherapeutic Protection Against Infection

Microbiome-targeted biotherapies protect against infection not through a single pathway but through interconnected ecological, metabolic, epithelial, and immunological mechanisms. Their effects can include restoration of microbial niches, restriction of pathogen access to nutrients and attachment sites, production of inhibitory metabolites and antimicrobial factors, reinforcement of the intestinal barrier, and regulation of host immune responses. These mechanisms are functionally interconnected: microbial metabolites can simultaneously influence pathogen fitness, epithelial integrity, and immune signaling, while host-derived factors can reshape microbial competition and nutrient availability. Recent work therefore supports viewing biotherapeutic protection as restoration or enhancement of an integrated host–microbiome defense network rather than simple replacement of individual bacterial taxa (Jones *et al.*, 2025; Li and Guo, 2026).

Restoration of Colonization Resistance

A central mechanism of biotherapeutic protection is restoration of colonization resistance, whereby a functionally competent microbial community prevents invading or opportunistic organisms from establishing and expanding. Biotherapeutic interventions can restore ecological occupancy, microbial diversity, metabolic competition, and cross-feeding networks that are disrupted by antibiotics, disease, or other perturbations. Competition for spatial niches and essential substrates—including carbohydrates, amino acids, oxygen, and other electron acceptors—can deprive pathogens of the resources required for expansion. Recent evidence demonstrates that colonization resistance is highly context dependent and emerges from interactions among microbial composition, metabolism, host physiology, and the intestinal environment rather than from the presence of a single "protective" organism (Woelfel *et al.,* 2024; Jones *et al.,* 2025). Restoration of these ecological constraints is particularly relevant to infections caused by resistant organisms. Defined microbial communities can reconstruct metabolic networks that consume nutrients otherwise available to pathogens, while specific commensals can occupy ecological niches required by multidrug-resistant organisms. For example, recent evidence indicates that microbial depletion of particular carbon sources can restrict pathogen growth, whereas disruption of commensal communities can release previously inaccessible metabolic niches and facilitate pathogen expansion. Thus, effective biotherapy may restore colonization resistance by recovering community-level ecological functions, rather than simply increasing microbial diversity (King *et al.,* 2025; Li and Guo, 2026).

Pathogen Inhibition and Competitive Exclusion

Beyond occupying ecological niches, beneficial microorganisms can directly suppress pathogens through nutritional competition, antimicrobial production, contact-dependent antagonism, and metabolite-mediated inhibition. Competition for carbon sources, amino acids, iron, and other limiting substrates reduces pathogen fitness, whereas bacteriocins, antimicrobial peptides, short-chain fatty acids (SCFAs), and secondary bile acids can inhibit pathogen growth or survival. Contact-dependent systems, including type VI secretion systems and related antibacterial mechanisms, provide an additional means of eliminating competing organisms within densely populated microbial communities. These mechanisms are particularly important because they can generate selective ecological pressure against pathogens without broadly eliminating the surrounding microbiota (Deng and Wang, 2024; Li and Guo, 2026). Microbial metabolites further connect competition with pathogen physiology. SCFAs can lower luminal pH, alter bacterial metabolism, and directly inhibit susceptible pathogens, while secondary bile acids can interfere with pathogen germination and growth. Importantly, these effects are not universally inhibitory; their activity depends on metabolite concentration, microbial community composition, pathogen metabolic capacity, and intestinal conditions. This context dependence is increasingly recognized as a critical determinant of therapeutic efficacy and supports the development of biotherapies that restore specific metabolic functions rather than relying exclusively on taxonomic replacement (Jones *et al.,* 2025; Yu *et al.,* 2026).

Enhancement of Intestinal Barrier Function

The intestinal barrier represents a second major layer of protection against infection and comprises the mucus layer, epithelial cells, tight-junction complexes, antimicrobial molecules, and underlying immune components. Microbiome-modulating biotherapies can strengthen this barrier by increasing mucus production, maintaining epithelial integrity, regulating tight-junction proteins, and promoting epithelial repair. Microbial metabolites are particularly important mediators because they translate changes in microbial activity into epithelial responses. SCFAs, for example, can influence tight-junction organization, MUC2 production, epithelial energy metabolism, and antimicrobial peptide expression, thereby reducing permeability and limiting pathogen access to host tissues (Chen *et al.,* 2025; Yu *et al.,* 2026). Barrier protection also depends on maintaining appropriate communication between epithelial cells, microbial communities, and mucosal immune cells. Disruption of this interaction can increase permeability, facilitate microbial translocation, and amplify inflammation, creating conditions that favor pathogen persistence. Conversely, restoration of microbiota-derived metabolic signals can support epithelial homeostasis and reinforce the physical and chemical barriers separating luminal microorganisms from host tissues. Accordingly, barrier enhancement represents an important mechanism through which microbiome-based interventions may convert ecological restoration into measurable protection against infection (Okumura and Takeda, 2025; Chen *et al.,* 2025).

Modulation of Host Immune Responses

Biotherapeutic protection also involves bidirectional regulation of mucosal immunity. The microbiota continuously supplies molecular signals and metabolites that influence epithelial cells, dendritic cells, macrophages, innate lymphoid cells, T cells, and B cells. Appropriate microbial stimulation can enhance antimicrobial defense while maintaining immune tolerance toward beneficial resident organisms. Microbiota-derived metabolites, particularly SCFAs, can regulate immune-cell differentiation and function through G-protein-coupled receptors and epigenetic mechanisms, influencing regulatory T-cell responses, cytokine production, antimicrobial peptide expression, and mucosal antibody responses (Yu *et al.,* 2026). The IL-22 axis provides an important example of microbiota–immune cooperation. Microbial signals can promote dendritic-cell and ILC3 pathways that regulate IL-22 production, which subsequently influences epithelial antimicrobial defenses, glycosylation, mucus-associated protection, and microbial nutrient availability. This creates a feedback system in which host immunity not only responds to microbes but also shapes the ecological environment in which microbial competition occurs. Such reciprocal regulation explains why successful microbiome restoration can have effects extending beyond pathogen exclusion to broader improvement of mucosal immune competence (Li and Guo, 2026).

Suppression of Pathogen Virulence and Antimicrobial Resistance

An important emerging mechanism is the ability of microbiome restoration to constrain pathogen virulence and antimicrobial resistance (AMR) by altering the ecological and metabolic conditions that support pathogen fitness. Microbial metabolites can influence pathogen signaling, metabolic pathways, biofilm formation, and expression of virulence-associated genes. For example, recent evidence indicates that microbiota-derived metabolites can interfere with virulence regulation, while changes in nutrient availability may determine whether pathogens remain metabolically constrained or exploit newly available resources following microbiome disruption (Jones *et al.,* 2025). Microbiome integrity is also relevant to AMR because dysbiosis can create ecological reservoirs that favor expansion, persistence, and dissemination of resistant organisms. Antibiotic-induced depletion of commensals can increase nutrient availability and reduce inhibitory metabolites, thereby facilitating resistant-pathogen colonization. Conversely, microbiome restoration may reduce the ecological fitness of resistant organisms through nutrient competition, antimicrobial metabolites, niche exclusion, and reduced opportunities for persistence and transmission. However, biotherapeutic modulation should not be interpreted as universally eliminating resistance genes;

rather, its principal potential lies in reducing the ecological success, expansion, and dissemination of resistant pathogens (Ahmad *et al.,* 2025; Sharma *et al.,* 2025).

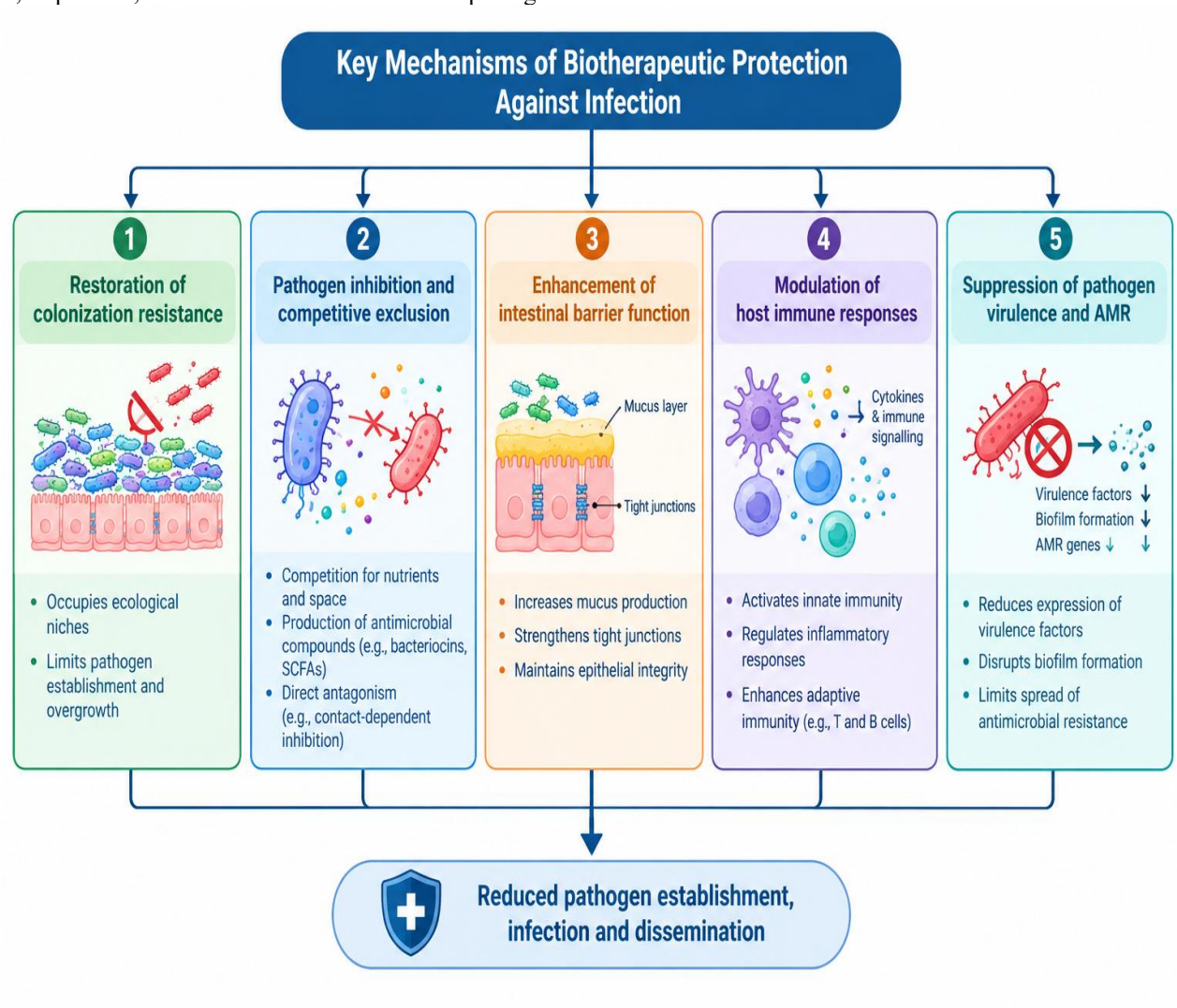


Figure 2. Key mechanisms of biotherapeutic protection against infection. Microbiome-targeted biotherapies can protect against infection through five interconnected mechanisms: restoration of colonization resistance, pathogen inhibition and competitive exclusion, enhancement of intestinal barrier function, modulation of host immune responses, and suppression of pathogen virulence and antimicrobial resistance. These mechanisms operate through ecological competition, antimicrobial metabolites, epithelial and mucus defenses, immune signaling, and altered pathogen fitness, collectively limiting pathogen establishment, proliferation, persistence, and dissemination.
Source: Li and Guo (2026)

Applications in Infectious Diseases

The clinical and translational applications of gut microbiome biotherapy are expanding from recurrent Clostridioides difficile infection (CDI) toward enteric bacterial infections, multidrug-resistant organism (MDRO) colonization, and infections caused by viruses, fungi, and parasites. However, the maturity of evidence differs substantially among these indications. Microbiome-based therapeutics have achieved their strongest clinical validation in recurrent CDI, whereas applications in MDRO decolonization and other infectious diseases remain predominantly investigational. This distinction is important because restoration of microbial functions does not necessarily translate into uniform pathogen clearance across diseases; therapeutic effects depend on pathogen ecology, host factors, microbial engraftment, and the specific functions restored by the intervention (Lynch *et al.,* 2025; Pitashny *et al.*, 2025).

Clostridioides *difficile* Infection

Recurrent CDI represents the most advanced infectious-disease application of microbiome-based therapy. Antibiotic exposure disrupts microbial diversity and metabolic networks

that normally restrict C. difficile germination and expansion. In particular, disruption of bile-acid metabolism and loss of competing microorganisms can create an ecological environment favorable to recurrent disease. Microbiome restoration therefore aims to re-establish colonization resistance rather than directly eradicate C. difficile through conventional antimicrobial activity (Lucky *et al.,* 2025). The therapeutic field has progressed from conventional fecal microbiota transplantation (FMT) toward standardized microbiota-derived products and defined live biotherapeutics. This transition addresses important limitations of donor-derived FMT, including compositional variability, manufacturing standardization, screening requirements, and uncertainty regarding the active therapeutic components. The success of purified spore-based products illustrates how defined microbial functions can reproduce clinically relevant aspects of microbiome restoration. In a phase 3 trial, SER-109 substantially reduced recurrence compared with placebo following standard antibiotic treatment, with microbiome engraftment accompanied by restoration of secondary bile-acid profiles associated with inhibition of C. difficile spore germination. Current evidence therefore supports microbiome therapeutics as an important strategy for preventing recurrence after treatment of CDI, particularly in patients with recurrent disease. Nevertheless, questions remain concerning patient selection, durability of engraftment, long-term safety, product composition, and the extent to which standardized products can reproduce the ecological complexity of conventional FMT (Lucky *et al.,* 2025; Pitashny *et al.,* 2025).

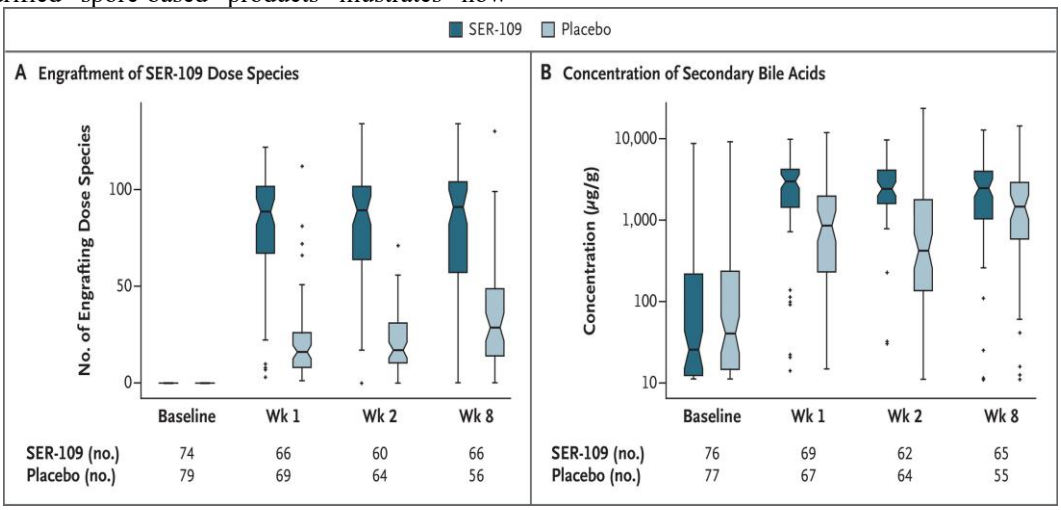


Figure 3. Compositional and metabolomic changes in the microbiome following SER-109 therapy for recurrent Clostridioides difficile infection. SER-109 administration promotes engraftment of microbiome species and restoration of secondary bile-acid metabolism, illustrating the ecological and metabolic changes associated with protection against recurrent CDI.Source: Feuerstadt *et al.* (2022)

Enteric Bacterial Infections

Beyond CDI, microbiome-based interventions have potential against enteric pathogens including Salmonella enterica, pathogenic Escherichia coli, and other gastrointestinal bacterial pathogens. Protection depends on the combined effects of microbial competition, nutrient depletion, inhibitory metabolites, antimicrobial products, epithelial defenses, and mucosal immune responses. Consequently, restoration of a functionally competitive microbiota may reduce pathogen establishment even when the intervention does not exert a conventional bactericidal effect (Kroon and Hardt, 2025).

Salmonella Typhimurium provides one of the best-characterized examples of this multilayered protection.

Commensal organisms can compete with Salmonella for essential nutrients, produce inhibitory metabolites such as short-chain fatty acids, and deploy bacteriocins or contact-dependent antibacterial systems. These microbial mechanisms operate alongside the mucus and epithelial barriers and innate and adaptive immune responses to create several sequential obstacles to infection. Kroon and Hardt (2025) emphasize that resistance to S. Typhimurium is therefore a multilayered property of the intestinal ecosystem, rather than an effect attributable to a single commensal species.

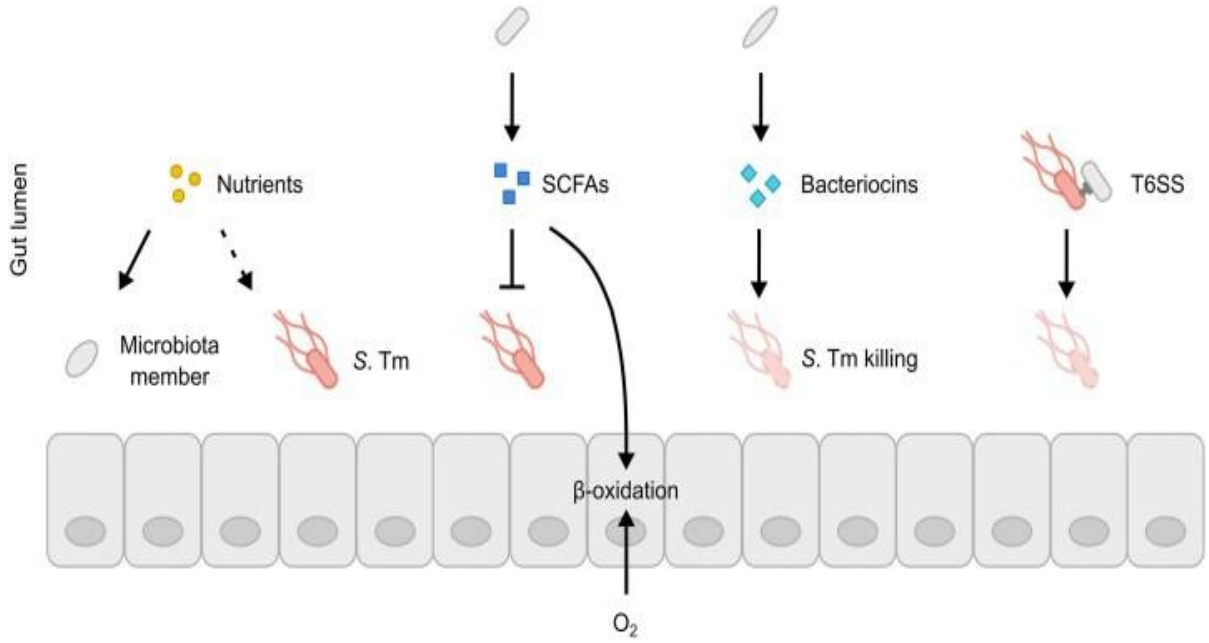


Figure 4. Microbiota-mediated colonization resistance against Salmonella Typhimurium. The intestinal microbiota restricts Salmonella Typhimurium colonization through complementary mechanisms, including competition for essential nutrients, production of inhibitory short-chain fatty acids, secretion of bacteriocins, and contact-dependent killing through type VI secretion systems. Together, these microbial interactions limit pathogen growth and establishment within the intestinal ecosystem.
Source: Kroon and Hardt (2025)

Multidrug-Resistant Bacterial Infections

The gastrointestinal tract represents an important reservoir for multidrug-resistant organisms, including carbapenem-resistant Enterobacterales and vancomycin-resistant enterococci. Intestinal carriage may precede extraintestinal infection and provides opportunities for resistant organisms to disseminate to vulnerable patients and healthcare environments. Consequently, microbiome-based interventions are increasingly being investigated not only as treatments for infection but also as decolonization strategies designed to reduce intestinal pathogen carriage before invasive disease occurs (Sharma *et al.,* 2025; Abah *et al.,* 2026; Weirauch *et al.*, 2026). FMT, probiotics, live biotherapeutic products, bacteriophages, and other targeted microbiome interventions have all been explored for MDRO decolonization. Their proposed benefits include restoration of ecological competition, depletion of pathogen-accessible nutrients, production of inhibitory metabolites, and selective suppression of resistant organisms. However, clinical evidence remains heterogeneous, and large randomized controlled trials are still lacking for most approaches. The review by Weirauch *et al.* (2026) highlights this evidence gap and concludes that microbiome-modulating strategies are promising but cannot yet be regarded as established approaches for routine MDRO decolonization. An important consideration is that microbiome-based decolonization may offer an advantage over broad-spectrum antimicrobial eradication because it seeks to restore ecological resistance while minimizing additional disruption of the resident microbiota. Future approaches are therefore likely to combine microbiome restoration with highly selective interventions, such as bacteriophages or defined microbial consortia, to target resistant organisms while preserving beneficial microbial functions (Sharma *et al.*, 2025; Otota-Jumudjayen *et al.,* 2026; Weirauch *et al.*, 2026).

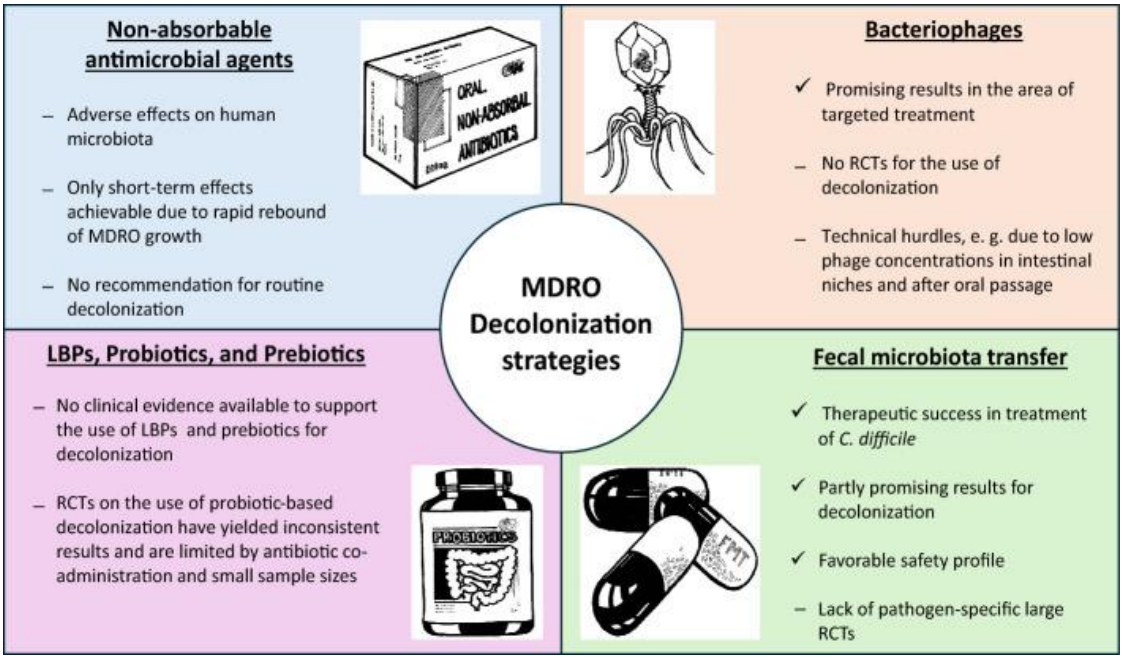


Figure 5. Gastrointestinal decolonization strategies for multidrug-resistant organisms. The gastrointestinal tract represents an important reservoir of multidrug-resistant organisms (MDROs). Current decolonization strategies include non-absorbable antimicrobial agents and emerging microbiome-directed approaches such as fecal microbiota transplantation, probiotics, live biotherapeutic products, prebiotics, and bacteriophages. Although microbiome-based approaches show promise for reducing MDRO carriage, current clinical evidence remains heterogeneous and large pathogen-specific randomized trials are still needed.
Source: Weirauch *et al.* (2026)

Viral, Fungal, and Parasitic Infections

The application of gut microbiome biotherapy to viral, fungal, and parasitic infections is considerably less mature than its application to recurrent CDI. Nevertheless, accumulating evidence indicates that microbiome composition and function can influence pathogen replication, mucosal barrier integrity, innate and adaptive immunity, and disease severity, creating opportunities for microbiome-directed prevention or adjunctive treatment.

Viral Infections

Interactions between the gut microbiome and enteric viruses are bidirectional. Microbial components can influence viral attachment, receptor availability, innate immune signaling, and epithelial susceptibility, while viral infection can alter microbial composition and metabolic activity. Probiotics and other microbiome-directed approaches have therefore been investigated as potential adjuncts to antiviral strategies, particularly through enhancement of mucosal immunity and barrier function (Borrego-Ruiz and Borrego, 2025; Malik *et al.*, 2025). Borrego-Ruiz and Borrego distinguish between microbiome activities that can promote and those that can restrict enteric viral infection. Their review highlights the influence of microbial components, metabolites, secretory IgA, epithelial interactions, and histo-blood-group-antigen-related mechanisms on viral infection.

Fungal Infections

The relationship between the bacterial microbiome and Candida albicans illustrates another potential application. Antibiotic-induced disruption of bacterial communities can reduce ecological competition and permit fungal expansion, while bacterial metabolites and interkingdom interactions can influence fungal morphology, biofilm formation, and virulence. Restoration of bacterial competitors may therefore contribute to fungal control through ecological exclusion, metabolite production, epithelial protection, and immune regulation (Song *et al.*, 2025). However, most evidence remains mechanistic or preclinical, and the clinical efficacy of microbiome-directed interventions for invasive candidiasis has not been established. This distinction is important because the biological plausibility of bacterial–fungal competition does not necessarily demonstrate therapeutic efficacy in patients.

Parasitic Infections

Gut microbiota–parasite interactions are similarly complex. Microbial communities can influence parasite establishment, nutrient availability, epithelial responses, and host immunity, while parasitic infections can reshape microbial composition. Probiotics, prebiotics, and other microbiome-modulating strategies are consequently being investigated as adjunctive approaches (Lynch *et al.*, 2025). Nevertheless, compared with CDI, the evidence base remains dominated by experimental

models and early-stage translational studies, and microbiome therapy should not currently be considered a replacement for established antiparasitic treatment. Overall, viral, fungal, and parasitic infections represent important emerging applications rather than clinically established indications. Further research should identify pathogen-specific microbial functions, define reproducible therapeutic formulations, and establish whether microbiome modulation improves clinically meaningful outcomes when combined with standard anti-infective therapy.

Table 3. Applications and translational status of gut microbiome biotherapies across infectious diseases

Disease	Applications	Translational status	Reference
Recurrent C. difficile infection	Microbiome restoration and prevention of recurrence	Clinically established	Lucky et al. (2025)
Enteric bacterial infections	Enhancement of colonization resistance and pathogen exclusion	Emerging / mainly experimental	Kroon and Hardt (2025)
Multidrug-resistant bacterial infections	Reduction of gastrointestinal MDRO carriage and dissemination	Investigational	Weirauch et al. (2026)
Viral infections	Modulation of viral susceptibility, replication and mucosal defense	Emerging / predominantly preclinical	Borrego-Ruiz and Borrego (2025)
Fungal infections	Suppression of fungal expansion through bacterial–fungal interactions	Early / preclinical	Song et al. (2025)
Parasitic infections	Modulation of pathogen burden and host–microbiome responses	Predominantly experimental	Lynch et al. (2025)

Across infectious diseases, microbiome biotherapy shows a clear gradient of translational maturity. Recurrent CDI has the strongest clinical evidence and has already reached standardized microbiome-based products. MDRO decolonization is a major translational target but remains investigational, while enteric bacterial infections have substantial mechanistic support but relatively limited therapeutic validation. Viral, fungal, and parasitic infections represent broader emerging applications in which microbiome–pathogen interactions are increasingly understood but therapeutic efficacy remains uncertain. This distinction should guide future development toward interventions supported by defined microbial functions, measurable biomarkers of response, and pathogen-specific clinical endpoints (Lynch *et al.,* 2025; Pitashny *et al.*, 2025; Weirauch *et al.*, 2026).

Clinical Evidence and Translational Challenges

Clinical evidence for gut microbiome biotherapies has progressed toward controlled trials of increasingly defined microbial products, with the strongest evidence currently available for recurrent Clostridioides difficile infection (rCDI). In the phase 3 ECOSPOR III trial, oral SER-109 significantly reduced recurrence compared with placebo, demonstrating that a defined microbiome-derived product could reproduce therapeutic effects previously associated with fecal microbiota transplantation (FMT) (Feuerstadt *et al.,* 2022). Similarly, the phase 2 CP101 trial reported favorable safety and tolerability while supporting its efficacy in preventing recurrent CDI (Allegretti *et al.,* 2025). Bethlehem *et al.* (2026) further compared a 15-strain live biotherapeutic product (MTC01) with FMT from the same donor; recurrence was prevented in 7 of 9 MTC01 recipients and 8 of 9 FMT recipients at 8 weeks, with substantial strain engraftment in both groups. These findings support the feasibility of replacing complex donor material with defined microbial communities. Nevertheless, efficacy varies according to strain composition, dose, manufacturing, administration route, disease phenotype, baseline microbiome, and host characteristics. This is particularly relevant to probiotics, where findings from one strain or formulation cannot necessarily be generalized. Quigley and Shanahan (2025) emphasize that probiotic evidence remains context-dependent, while Lynch *et al.* (2025) recommend evaluating next-generation microbiome therapeutics according to defined biological functions rather than broad intervention categories. Future trials should therefore combine clinical outcomes such as recurrence, pathogen clearance, hospitalization, antibiotic exposure, and mortality with microbiological, metagenomic, metabolomic, and strain-engraftment measures. Safety remains a major concern because these therapies contain living organisms or biologically active microbial material. Potential risks include transmission of pathogens or antimicrobial-resistance determinants, unintended engraftment, disruption of resident microbiota, horizontal gene transfer, and rare invasive infections. These concerns are particularly important for FMT and complex microbial preparations. Although CP101 and MTC01 provide encouraging short-term safety data, their limited sample sizes and follow-up cannot exclude uncommon or delayed adverse effects (Allegretti *et al.,* 2025; Bethlehem *et al.,* 2026). Long-term pharmacovigilance is therefore essential.

Standardization and manufacturing present additional barriers. Microbiome products require simultaneous control of identity, viability, purity, potency, genetic stability, and functional

activity. The Asia-Pacific Microbiota Consortium emphasizes strain-level characterization, genomic assessment, manufacturing consistency, safety testing, and appropriate critical quality attributes for live biotherapeutic products (Tseng *et al.,* 2025). Because taxonomic composition alone may not predict therapeutic activity, functional assays, metabolomics, and strain-resolved sequencing may be necessary to establish potency and consistency (Lynch *et al.,* 2025). Maintaining viability, strain composition, contamination control, and batch-to-batch reproducibility also requires specialized manufacturing processes (Slijkerman *et al.,* 2025). Although defined consortia provide greater compositional control than FMT, increasing strain numbers increases technical complexity, as demonstrated by MTC01 (Bethlehem *et al.*, 2026). Regulatory uncertainty further complicates translation because microbiome products do not always fit conventional pharmaceutical, biologic, food, or human-derived categories. European regulatory developments concerning substances of human origin have implications for donor-derived interventions, while defined live biotherapeutics raise additional questions regarding classification, potency, manufacturing, and clinical evidence (Rodriguez *et al.*, 2025). The European Medicines Agency's 2026 initiative on the non-clinical development and evaluation of microbiome-based medicinal products further highlights the need for microbiome-specific regulatory guidance (European Medicines Agency, 2026). Overall, successful translation will require well-characterized microbial strains or consortia, validated manufacturing, reliable potency assays, standardized clinical endpoints, rigorous safety monitoring, and regulatory harmonization. Future development is likely to move from nonspecific restoration of microbial diversity toward precision therapies targeting defined ecological or metabolic functions. Integrating microbial composition with functional biomarkers and patient characteristics may improve patient selection and treatment monitoring (Lynch *et al.,* 2025; Tseng *et al.,* 2025; Abah *et al.,* 2026). Although defined live biotherapeutics and controlled trials demonstrate important progress, stronger evidence is still required before microbiome biotherapy becomes routine in anti-infective practice.

Table 4. Major clinical and translational challenges in gut microbiome biotherapy

Challenges	Major concern	Translational priority
Clinical efficacy	Variable outcomes among diseases, products, strains, and patients	Larger, well-controlled trials with clinically meaningful endpoints
Safety	Pathogen transmission, antimicrobial-resistance genes, unintended engraftment, and long-term effects	Rigorous screening and long-term surveillance
Standardization	Variable composition, viability, and biological activity	Defined strains/consortia and validated critical quality attributes
Manufacturing	Maintaining viability, purity, stability, and batch reproducibility	Scalable GMP-compatible production and process validation
Potency assessment	Taxonomic composition may not reflect therapeutic function	Functional, metabolomic, and strain-level assays
Regulations	Evolving and heterogeneous regulatory classifications	Microbiome-specific and internationally harmonized frameworks

Adapted from Slijkerman *et al.* (2025); Bethlehem *et al.* (2026)

Emerging Directions and Future Prospects

The future of gut microbiome biotherapy is moving from broad microbiome restoration toward precision and function-oriented interventions. Advances in metagenomics, metabolomics, transcriptomics, and artificial intelligence are increasingly enabling identification of microbial functions, prediction of treatment responses, and patient stratification. Because microbiome composition varies considerably between individuals, precision approaches could use baseline microbial composition, antimicrobial-resistance profiles, metabolic activity, and clinical characteristics to select appropriate strains, consortia, or microbiome-modulating interventions (Haiser and de Gruijl, 2025; Kumar *et al.,* 2026). Multi-omics integration and computational modelling may therefore support personalized treatment selection and monitoring, although standardized sampling, functional validation, and clinical validation remain necessary (Lim *et al.*, 2025; Kumar *et al.,* 2026). Engineered microorganisms and bacteriophages represent another important frontier. Synthetic biology can generate microbial strains or consortia with defined functions, including pathogen inhibition and therapeutic-molecule production, potentially overcoming some limitations of conventional probiotics and FMT (Mkilima, 2025). CRISPR–Cas technologies may enable selective elimination or modification of pathogenic bacteria while minimizing disruption of beneficial microbiota (Benz *et al.,* 2025). Similarly, engineered bacteriophages can provide targeted antibacterial activity through modification of host range, antibacterial potency, or therapeutic payloads (Cao *et al.*, 2025; Skurnik *et al.,* 2025). However, phage therapy remains limited by strain specificity, bacterial resistance, pharmacokinetics, manufacturing, and regulatory challenges,

making personalized phage selection and standardized development particularly important (Moon *et al.,* 2025; Sinclair *et al.*, 2026). Integration with conventional antimicrobial therapy may provide a complementary strategy rather than replacing antibiotics. Microbiome-based interventions could reduce antibiotic-associated ecological damage and support restoration of colonization resistance, while phage–antibiotic combinations may enhance bacterial killing, disrupt biofilms, and potentially limit resistance development (Supina and Dennis, 2025; Wang *et al.,* 2025). However, these interactions may be synergistic or antagonistic depending on the pathogen, phage, antibiotic, dose, and treatment sequence, requiring rational optimization rather than empirical combination (Moon *et al.,* 2025; Supina and Dennis, 2025). Pharmacommicrobiomics may further improve antimicrobial selection by accounting for microbial effects on drug metabolism, efficacy, and toxicity (Ebadpour *et al.*, 2025). Overall, precision microbiome profiling, engineered microbial and phage platforms, and rational combination with antimicrobials are likely to shape the next generation of anti-infective therapy, provided that clinical validation, standardized manufacturing, safety monitoring, and appropriate regulatory frameworks continue to advance.

Conclusion

Gut microbiome biotherapy represents a promising shift from conventional pathogen-directed treatment toward restoration and targeted modulation of the microbial ecosystem that contributes to colonization resistance, immune regulation, and host protection. Current evidence demonstrates the greatest clinical maturity in recurrent Clostridioides difficile infection, while emerging approaches involving defined microbial consortia, live biotherapeutic products, probiotics, bacteriophages, engineered microorganisms, and microbiome-derived metabolites are expanding the therapeutic landscape. Despite this progress, broader clinical application remains limited by interindividual microbiome variability, incomplete understanding of mechanisms, safety concerns, inconsistent product composition, manufacturing challenges, and evolving regulatory requirements. Future research should therefore prioritize precision microbiome profiling, function-based therapeutic design, standardized manufacturing, robust clinical trials, and long-term safety monitoring. Ultimately, integrating microbiome modulation with conventional antimicrobial therapy may provide more effective and sustainable strategies for preventing infection, reducing recurrence, limiting antimicrobial resistance, and preserving microbial ecosystem stability. With continued advances in precision medicine and microbial engineering, gut microbiome biotherapy has the potential to become an important component of future infectious-disease prevention and treatment.

Authors' Contributions

The authors of this research have significantly contributed to the study's conception, data collection, and manuscript development. All authors were involved in writing the manuscript or critically reviewing it for its intellectual value. They have reviewed and approved the final version for submission and publication and accepted full responsibility for the content and integrity of the work.

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Conflict of Interest

The authors declared that there are no conflicts of interest.

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