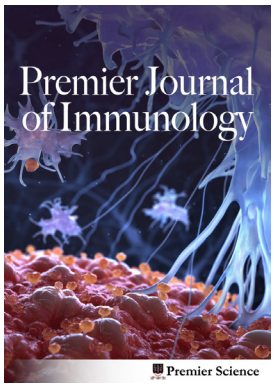

The Role of the Gut Microbiome in Infectious Diseases: Mechanisms, Diagnostics, and Therapeutic Potential

Riaz Ahmed

ABSTRACT

The human gut microbiome is based on the microbial ecosystem responsible for maintaining host health by regulating immune responses and providing resistance against pathogens. The narrative review explained the mechanisms by which the gut microbiome contributes to colonization of resistance, supports for mucosal immunity, and microbiome imbalance, thereby increasing the risk of infection. Moreover, the narrative review examines specific infections, including SARS-CoV-2, *Clostridioides difficile*, norovirus, and HIV. There is a discussion about the systemic impact of the microbiome through the gut-brain and gut-lung axes. The diagnostic advancement is also observed, including metagenomic sequencing and biomarkers of the microbiome. This review examined the systemic impact of the microbiome through the gut-lung and gut-brain axes. There have been observed diagnostic advancements, including microbiome biomarkers and metagenomic sequencing, which are being evaluated for their potential in early infection risk prediction and personalized medicine. Therapeutic approaches, such as faecal microbiota transplantation, probiotics, postbiotics, and engineered microbes, are effective in their clinical applications. The review has highlighted critical challenges of safety, host-specific responses, regulation, and long-term efficacy. The paper emphasized the gut microbiome's central role in infectious disease management and highlighted the need for further research to develop effective, personalized, and microbiome-based diagnostics.

Keywords: Gut microbiome, Colonization resistance, Mucosal immunity, Faecal microbiota transplantation, Microbiome biomarkers

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Introduction

Gut Microbiome: Composition and Function

According to the report,[1] the human gut microbiome comprises trillions of microorganisms, including bacteria, fungi, viruses, and archaea, which reside in the colon. These microbes are ten times more abundant than human cells, and they can code the gut microbiota, known as the microbiome, which is approximately 100 times more numerous.[2] Furthermore,[3] added that the microbiome has a complicated microbial community that plays an important role in maintaining the physiological homeostasis of the host. This leads to managing crucial functions such as vitamin synthesis, digestion, immune modulation, and maintaining the gut barrier integrity.[4] Dominant bacterial phyla, namely Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria, work synergistically in metabolic and immunological processes, continuously interacting with host cells and dietary substrates.[5,6] These interactions form the basis of the gut's ability to influence both local and systemic health.

Overview of Gut Microbiome Link to Infectious Diseases

Researchers[7,8] identified a profound connection between gut microbiota and infectious diseases. Dysbiosis is an imbalance in microbial composition that is increasingly associated with heightened susceptibility to infections, particularly those affecting mucosal surfaces.[9] However,[8,10] added that the gut microbiome impacts pathogen resistance by modulating mucosal immunity, constructing antimicrobial peptides, and competing with pathogens for nutrients and niche space. Additionally, microbiome modifications are observed in infections such as *Clostridioides difficile*, HIV, SARS-CoV-2, and norovirus, highlighting their diagnostic and prognostic relevance.[11] The connection between the gut and other organs through axes like the gut-lung and gut-brain pathways leads to connecting the microbiome in immune responses and systemic infections (Figure 1).[6]

Purpose of the Narrative Review

This narrative review aims to synthesize the current understanding of the gut microbiome's role in infectious diseases. It will concentrate on four main areas, including the microbial community's influence on disease susceptibility and progression, mechanisms of microbiome-host-pathogen interactions, the diagnostic utility of microbiome profiling, and therapeutic potentials such as faecal microbiota transplantation (FMT), probiotics, postbiotics, and engineered microbes.

The research objectives for the current narrative review are:

1. To analyze gut microbiota influence on susceptibility and progression of infectious diseases
2. To scrutinize microbial-pathogen interactions, immunological consequences, and the diagnostic potential of microbiome profiling in infectious disease management
3. To discover microbiome-based interventions, including probiotics, prebiotics, FMT, and engineered microbes
4. To identify research gaps and propose directions for clinical translation

Research Methodology

This study employed a structured narrative review approach to compile and analyze global evidence related to neglected tropical diseases (NTDs), with a focus on

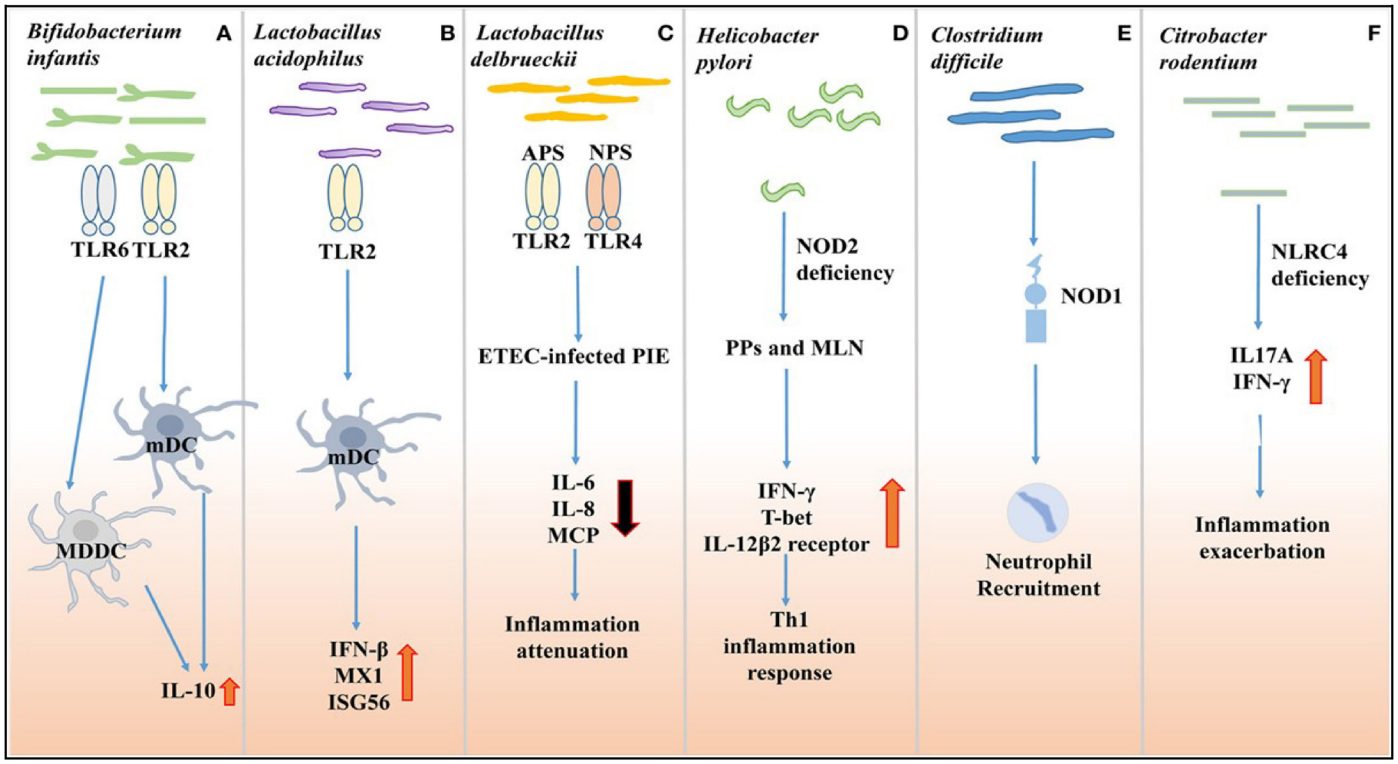

Fig 1 | Effects of gut microbes on innate immune receptors[4]

their overall burden, ongoing control efforts, and existing research gaps. A comprehensive literature search was conducted using four major academic databases: PubMed, Web of Science, Scopus, and Google Scholar (refer to Table 1). In addition to peer-reviewed journal articles, relevant documents published by the World Health Organization and major international donors or partners from January 2007 to May 2025 were also included in the review.

The search strategy incorporated Boolean logic, using combinations such as:

- ("neglected tropical diseases" OR "NTDs") AND (burden OR disability-adjusted life year [DALY] OR elimination OR control OR mass drug administration [MDA] OR research gaps OR vaccine OR diagnostics).
- Only studies published in English were considered for inclusion. To ensure relevance and quality, sources were selected if they met at least one of the following criteria:
  - Presented empirical data on the disease burden (e.g., DALYs, prevalence),
  - Evaluated or described NTD control strategies (e.g., MDA, water sanitation and hygiene, vector management),
  - Explored research innovations, such as new diagnostic tools, vaccine development, or digital health applications.

Microbiome-Host-Pathogen Interactions

Colonization Resistance

Colonization resistance is defined as the protective role of the gut microbiota in preventing pathogenic microorganisms from establishing in the gastrointestinal (GI) tract.[12] Another report[13] clarified that the process is facilitated by various organisms, such as commensal bacteria, competing with pathogens for physical niches and nutrients that limit the resources available for pathogens' growth. In this case, the antimicrobial compounds are produced by beneficial microbes like bacteriocins and short-chain fatty acids (SCFAs) that inhibit the invading pathogens (Figure 2).[14]

Investigators[15] added that the epithelial barrier integrity is increased by microbiota, which further controls the host immune responses by creating an inhospitable environment for destructive organisms. Another study[16] found that individuals with healthy microbiomes do not face infections with *C. difficile* that occur after using antibiotics and disrupt microbes' communities.[16] Similarly, the resistance towards colonies typically protects from intestinal infection, and this acts in the systemic immunity to reinforce microbial balance and maintain health.

Role in Mucosal Immunity

Mucosal immunity is developed and regulated by the gut microbiome.[6,8,12] It plays a vital role in educating the immune system from early life, assisting in distinguishing between harmful pathogens and harmless antigens. Moreover, commensal microbes stimulate the production of immunoglobulin A (IgA), which binds to pathogens and reduces their adherence to the intestinal epithelium. They also impact the differentiation of the T-cell population, specifically regulatory T-cells, which are crucial in maintaining immune tolerance,

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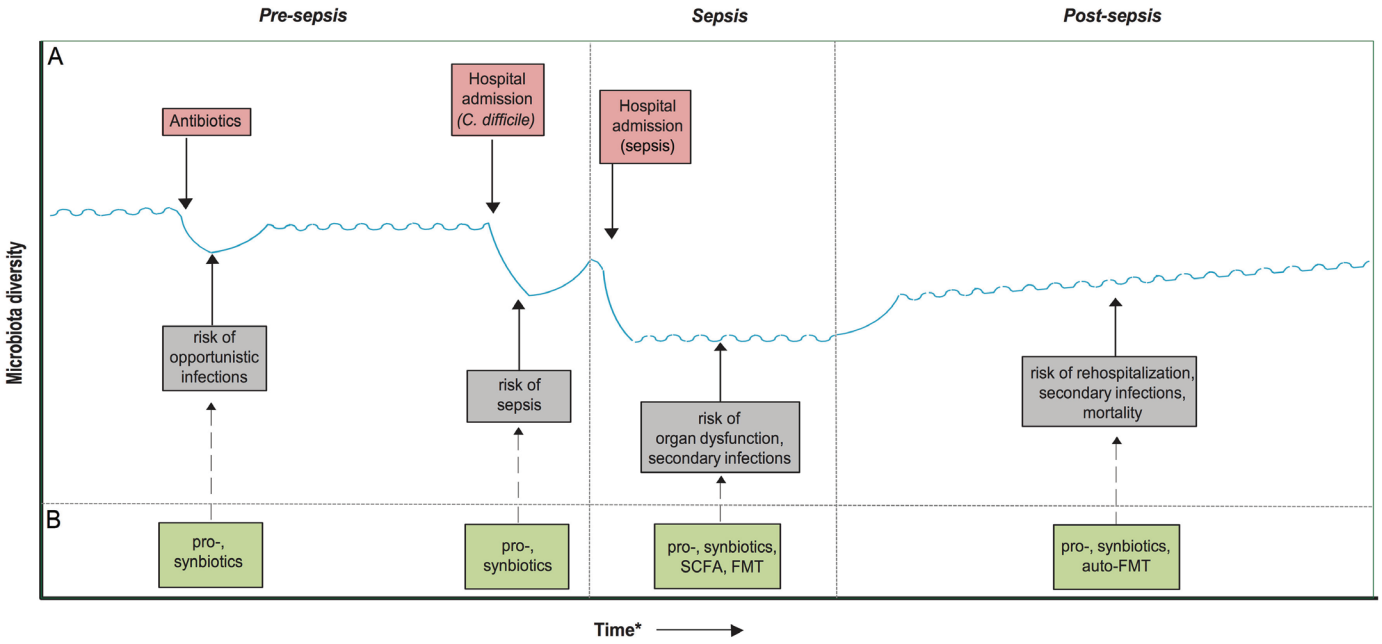

Fig 2 | Potential microbiota-associated intervention timeline[2]

and Th17 cells, which play a vital role in mucosal defense.[4] Moreover, microbial metabolites like butyrate also increase the epithelial barrier function and effective immune reaction towards pathogens, and they avoid excessive inflammation that can lead to tissue damage.[17] The disruption of the microbial signals because of factors like dietary or antibiotic changes can damage mucosal immunity, and it also increases susceptibility to GI and systemic infections, indicating the immunological importance of the microbiome.[4,6]

Dysbiosis and Increased Infection Risk

It was reported[18] that dysbiosis is an imbalance in the function or composition of gut microbiota, closely associated with increased vulnerability to infectious disease. It usually involves reducing the beneficial microbial population, overgrowth of opportunistic pathogens, and a loss of microbial diversity.[19] Such disruption directly weakens colonization resistance and damages mucosal immunity, allowing pathogens to attack more easily. Antibiotic-induced dysbiosis is a primary risk factor for *C. difficile* infection (CDI), where the absence of microbial competition allows pathogens to colonize and produce toxins.[11] Furthermore, dysbiosis also impacts immune homeostasis, which leads to either suppressing the immune responses or chronic inflammation that creates a favorable condition for infections.[20] In addition, microbial imbalance can also impact systemic immunity through gut-brain and gut-lung axes, thus contributing to neurological and respiratory infections.

Microbiome in Specific Infectious Diseases

C. difficile, HIV, SARS-CoV-2, Norovirus

The primary role of the gut microbiome is to modulate host susceptibility, clinical outcomes, and immune responses in a wide range of infectious diseases. In the case of infectious pathogens, CDI is studied extensively about gut dysbiosis.[21] In addition, CDI also raises the broader issue of antibiotic use that disrupts the commensal balance of microbes and minimizes resistance to colonization. It allows *C. difficile* spores to proliferate and germinate, producing toxins that lead to colitis and inflammation.[22] Furthermore, clinical symptoms in these cases range from mild diarrhea to life-threatening pseudomembranous colitis. An effective treatment for recurrent CDI is FMT, as it restores the microbial diversity and competitive exclusion of pathogens.[23] The successful treatment through FMT has highlighted the therapeutic potential of microbiome modulation.

On the other hand, in HIV infections, earlier changes are detected in the gut microbes, even before the immune decline.[24] Gut-associated lymphoid tissue (GALT) by HIV led to compromised epithelial integrity and increased permeability of the intestine (Figure 3). Such disruption also facilitates the translocation of microbes, allowing bacteria and their products to enter the bloodstream and trigger chronic systemic inflammation. Despite effective antiretroviral therapy, some individuals with HIV experience a changed gut microbiota characterized by a reduction in beneficial taxa (Lactobacillus and Bifidobacterium) and an increase in pro-inflammatory species (*Prevotella*).[25] Such shifts are linked with immune activation, and this contributes towards non-AIDS-related comorbidities, including neurocognitive and cardiovascular disorders. The virus responsible for COVID-19, SARS-CoV-2, also shows a bidirectional interaction with the gut microbiome.[26]

Researchers[26,27] have demonstrated that COVID-19 patients exhibit significant microbial alterations, including the enrichment of opportunistic pathogens such as *Enterococcus* and the depletion of

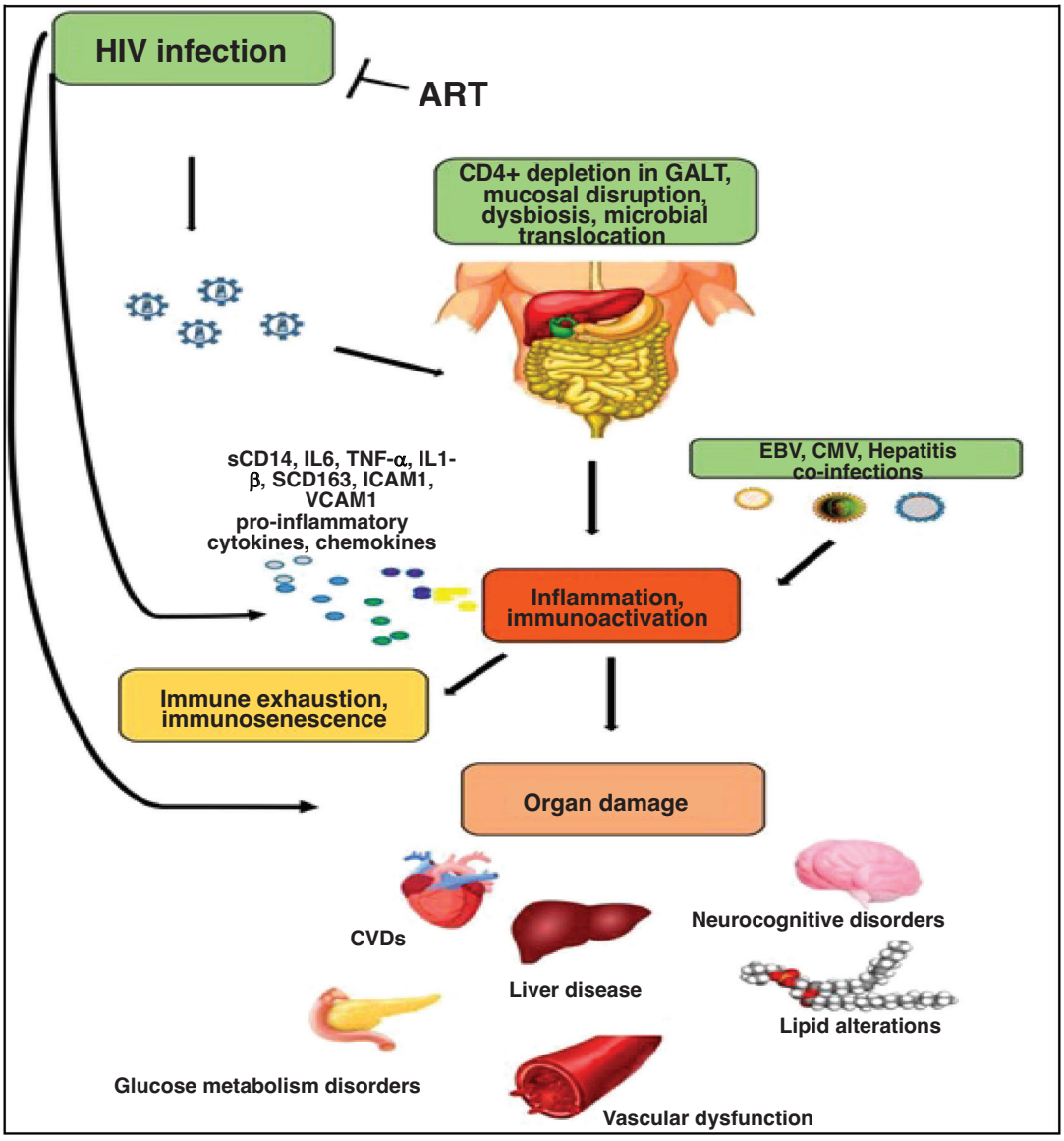

Fig 3 | Systemic outcomes of HIV infection in the GALT

Faecalibacterium prausnitzii.[27] Such changes were correlated with the severity of disease, prolonged viral shedding, and systemic inflammation. Furthermore, SARS-CoV-2 also infects intestinal epithelial cells through ACE2 receptors, leading to gastrointestinal symptoms in a subset of patients.[27] Furthermore, the extent of dysbiosis usually impacts the immune response and the recovery trajectory.

Viral gastroenteritis is commonly caused by norovirus as it interacts with gut microbiota during infections.[28] In this action, commensal bacteria are observed to facilitate norovirus application that depends on the microbial context.[29] A change in microbiota can impact viral infectivity as well as the shedding duration.

Gut-Lung and Gut-Brain Axis

According to the report,[30] the gut-lung and gut-brain axes are emerging areas where studies are focusing on the gut microbiota's influence on systemic infections and distant organs. Furthermore, the gut-lung axis is defined as a bidirectional communication between the GI tract and the respiratory system that is primarily facilitated by microbial metabolites, shared mucosal immunity, and immune signalling.[31] The gut microbiota disruption can harm lung immunity and increase susceptibility to respiratory infections like COVID-19 and influenza. For example, SARS-CoV-2 patients with dysbiosis are associated with an exacerbation of systemic inflammation and pulmonary symptoms.[27] Furthermore, probiotic interventions target the gut, and these are observed to be promising in increasing respiratory and immune defense.

Conversely, the gut-brain axis encompasses the complex neuroimmune interactions influenced by gut microbes.[32] Metabolites derived from microbiota, like SCFAs and neurotransmitter-like molecules, can directly cross the blood-brain barrier or impact the vagus nerve, which directly influences health.[33] In infections like HIV, gut dysbiosis leads to cognitive

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decline and neuroinflammation.[24] Moreover, systemic inflammation caused by gut microbial imbalance can worsen neurological symptoms in long COVID or viral encephalitis.[26] These axes identify the systemic actions of gut microbes beyond the intestine, indicating that keeping the microbial balance is important to protect against infections that affect neurological and respiratory symptoms.

Diagnostic Applications

Microbiome Biomarkers for Infection Risk

Microbiome biomarkers are becoming increasingly valuable tools for assessing the risk of infections, directly informing clinical decision-making.[34] The diversity and composition of the gut microbiota can act as an early indicator of susceptibility to various infections. For example, in the case of reduced levels of Bacteroidetes and Firmicutes with increased presentation of proteobacteria, which is frequently linked with increased risk of infections like sepsis and *C. difficile*.[35]

Biomarkers derived from microbial metabolites such as SCFAs, bile acids, and tryptophan derivatives can also reflect immune status and mucosal integrity.[36] Elevated or diminished concentrations of these metabolites may predict host vulnerability to both intestinal and systemic infections. Additionally, microbial gene expression profiles can offer functional insights into dysbiosis and immune dysfunction.[37] Advancements in microbiome biomarker research are driving the development of predictive diagnostic panels that stratify patients by infection risk or likely treatment response.[34] Such tools hold promises in hospital settings, where identifying at-risk patients early can inform antibiotic stewardship, infection control measures, and personalized interventions.[37] However, challenges remain in standardizing biomarker thresholds and accounting for host-specific and environmental variability (Figure 4).

Use of Metagenomics and Sequencing

Researchers[38,39] have indicated that metagenomics and next-generation sequencing (NGS) have transformed research related to the microbiome, enabling the culture-independent and comprehensive analysis of microbial communities. Such tools enable clinicians and researchers to identify and quantify thousands of microbial genes and species directly from clinical samples.[38] Furthermore, shotgun metagenomics provides higher resolution data about microbial functional capacity and taxonomy that makes it irreplaceable to detect potential pathogens and dysbiosis, even present in lower amounts, and that is previously unknown.[40] In the diagnosis of infectious diseases, metagenomics can reveal microbial signatures that predict susceptibility to infections and response to treatment. For example, sequencing the gut microbiome of immunocompromised patients can help detect opportunistic infections and antibiotic-resistant strains. Furthermore, longitudinal sequencing facilitates the monitoring of changes in the microbiome over time, providing insight into therapeutic effects and disease progression.

Similarly, NGS-based approaches also support the identification of microbial-derived metabolites and biomarkers associated with immune modulation and functional barriers.[39] The advancements in bioinformatics are increasing the accuracy and speed of data interpretation, making it unique and accessible for clinical usage. On the other hand, complex data analysis, higher costs, and sequencing protocol variability reduce the widespread implementation.[41] Even in the presence of such barriers, there is immense potential in the form of diagnostic tools for personalized infectious disease risk assessment and management.

Therapeutic Potential

FMT

According to the report,[23] FMT assists in transferring processed stool from a healthy donor into the GI tract of the patient to restore the microbial balance. The technique is emerging as a highly effective therapy for recurrent CDI with a higher success rate in patients who are unresponsive to antibiotics.[42] The treatment is dependent on the reintroduction of a functional and diverse microbial community that increases resistance to colonization, promotes mucosal healing, and suppresses pathogen overgrowth.[23] For broader infectious applications, FMT is applied for reducing antibiotic-resistant infections and gut dysbiosis management in immunocompromised patients. FMT also has the potential to improve immune reconstitution in HIV and modulate gut-lung axis activity in respiratory infections.[43]

Despite its promise, FMT faces significant challenges, including standardization of donor screening, processing protocols, and long-term safety.[44] Concerns over potential pathogen transmission and host-specific responses have led to increased interest in defined microbial consortia as alternatives to crude stool preparations. Nevertheless, FMT represents a paradigm shift in microbiome-targeted therapy, offering a novel, microbiota-based intervention for managing infectious diseases and promoting gut health in clinical settings.[23]

Probiotics, Postbiotics, Engineered Bacteria

Probiotics, postbiotics, and engineered bacteria represent a growing class of microbiome-based interventions designed to prevent or treat infectious diseases by modulating gut microbial communities.[45] Probiotics are live microorganisms that confer health benefits and are widely used to restore microbial balance following antibiotic treatment or GI infections. Specific strains, such as *Lactobacillus* and *Bifidobacterium*, have demonstrated efficacy in reducing the duration and severity of infections, including those caused by rotavirus and *C. difficile*, and enhancing mucosal immunity.[46] Postbiotics, the bioactive compounds produced by probiotics (short-chain fatty acids, bacteriocins, and enzymes), offer therapeutic benefits without introducing live organisms, which is particularly advantageous for immunocompromised individuals.[47] These compounds can modulate immune responses, reinforce gut barrier function, and inhibit pathogen colonization.

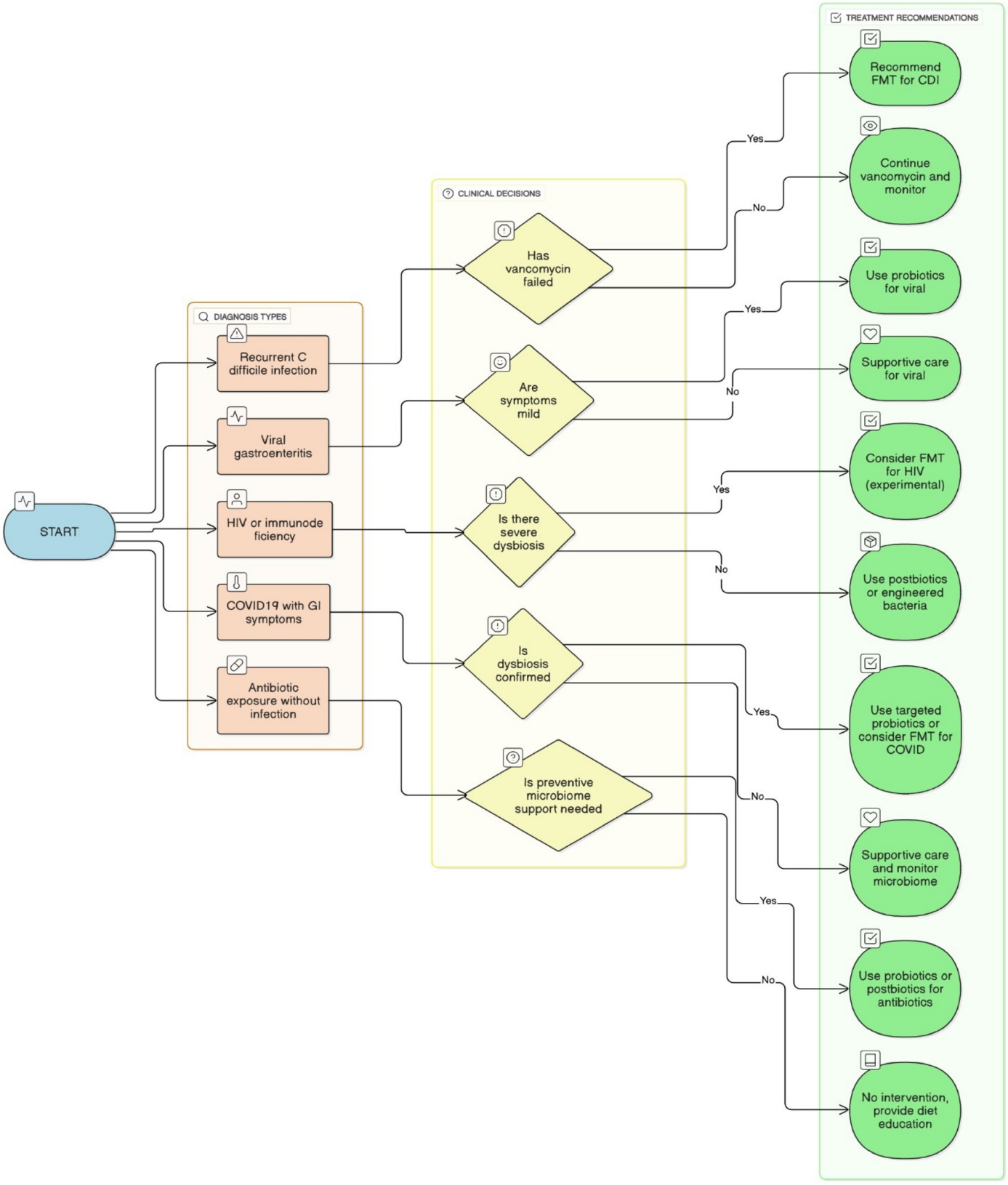

Fig 4 | Clinical decision tree: guiding microbiome-based interventions in infectious diseases

On the other hand, engineered bacteria are microbes that have been genetically modified to perform targeted therapeutic functions, such as delivering antimicrobial peptides, producing anti-inflammatory molecules, and sensing or neutralizing pathogens.[48] One example is the synthetic *Escherichia coli* strains created to detect the killing of *Pseudomonas aeruginosa* in animal models. These approaches can collectively offer

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Table 1 | Comparative analysis of therapeutic and diagnostic microbiome strategies

Aspect	FMT	Probiotics	Metagenomics	Culture-Based Diagnostics
Clinical Use	Primarily for recurrent CDI; also explored for multidrug-resistant infections and immune modulation[42,43]	Used for GI infections, antibiotic-associated diarrhea, and immune support[45,46]	Microbiome-wide profiling for infection risk, dysbiosis, and antibiotic resistance[38,39,40]	Detection of culturable pathogens, used in standard microbiology labs[38,41]
Success Rate	85–90% efficacy in recurrent CDI[23,42]	Usually, 30–40% efficacy in clinical trials; varies by strain and condition[45,46]	High accuracy and sensitivity in pathogen detection and gene profiling[38,39]	Lower sensitivity; misses non-culturable or low-abundance species[41]
Mechanism	Restores microbial diversity and function, reinforces colonization resistance and barrier integrity [23,43]	Introduces select strains (e.g., *Lactobacillus*, *Bifidobacterium*) to rebalance microbiota and stimulate immunity[46,47]	Captures microbial DNA directly; identifies taxonomic and functional genes[38,40]	Grows viable microbes on media; identifies morphology and antibiotic susceptibility[38,41]
Advantages	Highly effective, broad-spectrum microbiota restoration[23,42]	Safe for mild use, well-tolerated, commercially available[45,46]	Detects all microbes (including rare/unculturable); provides functional data[39,40]	Low cost, useful for antimicrobial resistance testing[38,41]
Limitations	Risk of donor variability, regulatory and safety challenges[43,44]	Limited strain diversity; inconsistent outcomes across individuals[45]	High cost, complex data analysis, not yet standardized in clinics[38,41]	Cannot detect fastidious, anaerobic, or rare microbes[41]

customizable, scalable, and safer alternatives for FMT. This requires further clinical trials to confirm efficacy, ensure safety, and optimize formulation, specifically regarding host-microbe interactions and long-term consequences.

Challenges and Future Directions

Safety, Personalization, Regulation

The clinical application of therapies targeting the microbiome is facing various challenges, including personalization, safety, and regulatory oversight. Safety concerns arise from adverse immune reactions, inadvertent pathogenic transmission, and horizontal gene transfer, particularly in treatments such as FMT.[23] The donor screening protocols assist in mitigating such risks, but this requires standardization. Furthermore, personalization increases complexity as individual microbiomes are highly variable and impacted by genetics, environment, diet, and health status.[16,25] The treatments effective for one patient may not suit others. Furthermore, tailored interventions need robust predictive biomarkers and microbial profiling that are not fully developed. Regulatory frameworks are slowly evolving for microbiome therapeutics, as they lack a clear classification due to their position between biologics and drugs. Such regulatory ambiguity interrupts market approvals and clinical translation. To address these challenges, interdisciplinary collaborations are needed for safe, well-regulated, and individualized microbiome treatment.

Long-Term Efficacy and Host-Specific Effects

Long-term efficacy and host-specific responses are significant challenges for microbiome-based interventions. However, various therapies, including FMT and probiotics, assist in short-term benefits, but their effects are usually uncertain.[43,44] Furthermore, recolonization can be temporary and restored, and the microbial communities can be disrupted again due to dietary factors, lifestyle changes, and additional treatments, such as the use of antibiotics. The host-specific factors, including immune status, age, genetics, and associated diseases, have a significant impact on the outcomes of treatment. On the other hand, probiotic strains are usually beneficial for one host; however, they may not have a similar effect on another host, or they may even become harmful to others due to differences in gut ecology and immune response.[47]

Moreover, the complexity of microbial interactions in the diverse ecosystem also makes it difficult to predict the long-term dynamics after interventions. It is essential to comprehend the configuration of beneficial microbiomes to achieve sustained therapeutic outcomes. Future research should focus on controlled trials, longitudinal studies, and systems biology approaches to uncover the factors that govern microbial resistance and compatibility with the host in the context of infection.

Conclusion

The gut microbiome regulates host immunity, influences susceptibility, and maintains mucosal integrity against a wide range of infectious diseases. Disrupting these compositions through diet, antibiotics, or illness can reduce colonization resistance and alter immune responses, thereby increasing the risk of infection. The current narrative review has highlighted particular pathogens, including HIV, *C. difficile*, norovirus, and SARS-CoV-2, that directly interact with the microbiome to shape outcomes and disease progression. Innovative methods are useful for predicting infection risk and tailored treatments. However, therapeutic interventions such as FMT, prebiotics, postbiotics, and engineered bacteria are more effective than complicated traditional treatments.

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