How can the gut microbiome be targeted to fight multidrug-resistant organisms?

Davido, B.; Merrick, B.; Kuijper, E.; Benech, N.; Biehl, L.M.; Corcione, S.; ESCMID

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Benjamin Davido, Blair Merrick, Ed Kuijper, Nicolas Benech, Lena M Biehl, Silvia Corcione, on behalf of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Host and Microbiota Interactions (ESGHAMI)

The rise of antimicrobial resistance presents a challenge to public health, undermines the efficacy of antibiotics, and compromises the management of infectious diseases. Gut colonisation by multidrug-resistant organisms, such as multidrug-resistant Enterobacterales and vancomycin-resistant enterococci, is associated with increased morbidity and mortality rates, as well as health-care costs. Of late, the role of the gut microbiome in combating colonisation by multidrug-resistant organisms, which could precede invasive infection, has garnered interest. Innovative interventions, including faecal microbiota transplantation, probiotics, phage therapy, and bacterial consortia, represent potential preventive or therapeutic options to counteract colonisation by multidrug-resistant organisms. In this Personal View, we have synthesised the current findings on these interventions and elucidated their potential as solutions to the crisis of antimicrobial resistance.

The microbiome and antimicrobial resistance

Microbiomes are intricately balanced ecosystems of microorganisms at various body sites and play pivotal roles in human health and disease. The gut microbiome, which constitutes by far the largest ecological niche in terms of organism and gene quantity, aids in digestion, synthesises vitamins, regulates the immune system, and has wide-ranging influences on metabolic and neurological functions.

Furthermore, the gut microbiome acts as a reservoir for antibiotic resistance genes (ARGs) and facilitates the transfer of resistance determinants among bacterial populations.[1] Exposure to antimicrobials can perturb the microbiome, disrupting microbial diversity and selecting for the expansion of enteric multidrug-resistant organisms (MDROs).[2,3] Notably, Gram-negative organisms, including extended-spectrum β-lactamase (ESBL)-producing Enterobacterales (ESBL-E), carbapenemase-producing Enterobacterales (CPE), and vancomycin-resistant enterococci (VRE), pose considerable challenges owing to their placement on the WHO critical priority list, reflecting their growing prevalence and the scant therapeutic arsenal available to address them.[4]

The role of the gut microbiome and its modification as a defence against MDROs is not well understood. Studies on the topic have often yielded contradictory results, most likely driven by the variability in the methodologies used to analyse the microbiome, in addition to the variety of MDROs studied.

Innovative approaches to combat antimicrobial resistance

Addressing antimicrobial resistance (AMR) requires a multifaceted approach that goes beyond traditional efforts for antibiotic development and stewardship. In 2019, clinical guidelines from the European Society of Clinical Microbiology and Infectious Diseases–European Committee on Infection Control on decolonisation of multidrug-resistant Gram-negative bacteria helped to identify the absence of any current approved therapeutic applications to eradicate MDROs from the intestinal tract.[5] Since then, several new promising approaches have emerged, with different levels of evidence available, each offering unique advantages and potential applications in clinical practice.

Faecal microbiota transplantation

Faecal microbiota transplantation (FMT) involves the transfer of minimally processed faeces from a healthy donor into the gastrointestinal tract of a recipient to restore microbial diversity. This intervention has proven efficacious for recurrent *Clostridioides difficile* infection (rCDI) and has potential application in combating MDROs by reducing ARGs.[6] One example is the study by Singh and colleagues, which reported successful decolonisation of MDROs following FMT, mediated by replenishing beneficial bacteria and restoring microbial equilibrium.[7]

Dinh and colleagues[8] further highlighted the potential benefits of FMT in restoring the gut microbiota and combating antibiotic-resistant infections, such as those caused by carbapenem-resistant Enterobacterales (CRE) and VRE. The authors emphasised that FMT could reduce the prevalence of ARGs in the microbiomes of individuals, thereby limiting the spread of resistance.[9] Similarly, Seong and colleagues[10] evaluated FMT for MDRO decolonisation in a population predominantly colonised with New Delhi metallo-β-lactamase (NDM)-producing *Klebsiella pneumoniae* and found a significant association between receipt of FMT and accelerated MDRO decolonisation, with effects observed in 205 days for healthy controls, but only in 42 days for patients who underwent FMT (p=0·007).

These observations are supported by the findings of a non-comparative prospective study by Hyun and colleagues, which showed that FMT in patients colonised with MDROs downregulated the expression of ARGs, especially that of *vanA*, and facilitated MDRO decolonisation.[11] Another recently published study showed that FMT in patients with rCDI reduced the ARG abundance without affecting the diversity of plasmid-mediated AMR or ARGs; the reduced

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Infectious Diseases Department, Raymond-Poincaré University Hospital, AP-HP, Paris-Saclay University, Garches, France (B Davido MD PhD); **Clinical Infection and Diagnostics Research Group, Guy's and St Thomas' NHS Foundation Trust and King's College, London, UK** (B Merrick MBChB); **Center for Microbiota Analysis and Therapeutics, Leiden University Center for Infectious Disease, Leiden University Medical Center, Leiden, Netherlands** (Prof E Kuijper MD PhD); **Hepato-Gastroenterology Department, Hôpital de la Croix-Rousse, Hospices Civils de Lyon, Lyon, France; Lyon GEM Microbiota Study Group, Lyon, France; Claude Bernard Lyon 1 University, Centre de Recherche en Cancérologie de Lyon (CRCL), Lyon, France** (N Benech MD PhD); **Department I of Internal Medicine, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany** (L M Biehl MD PhD); **German Centre for Infection Research (DZIF), Bonn-Cologne, Cologne, Germany** (L M Biehl); **Department of Medical Sciences, University of Turin, Torino, Italy** (S Corcione MD PhD); **Tufts University School of Medicine, Boston, MA, USA** (S Corcione)

Correspondence to:
Dr Benjamin Davido, Infectious Diseases Department, Raymond-Poincaré University Hospital, AP-HP, Paris-Saclay University, Garches 92380, France
benjamin.davido@aphp.fr

ARG abundance persisted for many years, suggesting a durable effect of the FMT.[12]

Uncontrolled studies do not account for spontaneous decolonisation of MDROs over time, which is a known occurrence.[13,14] To date, only two randomised clinical trials (RCTs) have evaluated MDRO eradication and FMT. The first, reported by Huttner and colleagues, showed that non-absorbable antibiotics followed by FMT decreased the ESBL or CPE carriage, as compared with that observed in the controls; however, this difference was not statistically significant, possibly due to the early termination of the trial.[15]

The second was reported by Woodworth and colleagues in a population of kidney transplant recipients.[16] FMT facilitated MDRO eradication, as compared with that observed in the controls, and reduced subsequent urinary tract infections caused by ESBL-E. This reduction in infection rates might be a more feasible and clinically relevant endpoint for FMT studies, as compared with long-term eradication. Similarly, a case-control study showed a significant reduction in MDRO-caused urinary tract infections and bloodstream infections following FMT.[17]

In 2024, Davido and colleagues showed that despite no statistical difference in the rate of complete CPE decolonisation between FMT-treated patients and a control group, the bacterial diversity and specific taxa are associated with the decolonisation of CPE after FMT, thus emphasising that numerous elements, including a possible biomass-effect, should be taken into account to observe a positive effect of FMT in the selected individuals.[18]

Despite promising results, FMT faces several challenges: regulatory frameworks need to address donor screening, product quality, and long-term safety monitoring to ensure the standardisation and acceptance of FMT in clinical practice.[19] The procurement of donor stool involves rigorous screening for pathogens and ARGs, a process that is both labour intensive and expensive. Storing stool samples is also challenging, as they need to be promptly processed and cryopreserved to maintain microbial viability, requiring specialised infrastructure and strict adherence to cold-chain protocols. Additionally, the mode of administration (whether through colonoscopy, enema, nasoenteric tube, or oral capsules) further influences the safety and comfort of the individual, in addition to the clinical outcomes.

In recent years, FMT has evolved and been implemented in various ways across different organisations and countries, with international guidelines established to standardise donor selection, stool preparation, and FMT procedures. However, the evidence supporting these standardised protocols is poor, and crucial factors such as thawing conditions, the addition of glycerol, and the effect of various pre-FMT antibiotics on treatment efficacy remain underexplored.[20]

Furthermore, the use of FMT for the decolonisation of MDROs has its specific challenges: inadequate harmonisation, insufficient evaluation of the cost-effectiveness of large-scale procurement, and the need for assessment of dose ranges for MDRO endpoints. Moreover, strategies that are effective for rCDI cannot be translated into daily routine for the control of AMR due to issues concerning the framework, logistics, and practicality.[21] From a long-term perspective, the potential of FMT for MDRO eradication will need to be compared with that of specifically developed live biotherapeutic products.

Dietary interventions

Diet plays a crucial role in shaping the structure and function of the gut microbiome. High-fibre diets promote the growth of commensals while inhibiting the expansion of pathobionts[22] and are associated with reduced carriage of ARGs.[23] Additionally, specific dietary components, such as polyphenols, can show antimicrobial properties and might inhibit MDRO proliferation.[24] Conversely, diets high in processed foods, saturated fats, and sugars disrupt the microbial balance and promote the growth of pathogenic bacteria, contributing to AMR.[25] Whether these effects are driven by nutritional content, the use of antimicrobials in livestock or meat, or both, or other factors need to be elucidated.[26] Despite dietary restrictions, vegans, vegetarians, and pescatarians have a similar resistome and MDRO carriage rate as those without dietary restrictions,[27,28] highlighting the need for further targeted investigations.

Dietary interventions with high fibre and fermented foods have been shown to increase microbiota diversity and positively modulate the immune status of human recipients.[29] Furthermore, recovery after antibiotic exposure has been shown to be influenced by fibre intake in a humanised mouse model.[30] The potential of such dietary interventions to improve resistance towards MDRO colonisation is yet to be studied, with at least one cross-sectional study underway examining associations between diet, gut microbiota, and MDROs.[31] With respect to VRE, data from mouse models suggest that lactose depletion attenuates the overgrowth of *Enterococcus*.[32] This finding has served as the rationale for introducing a lactose-free diet in a bone-marrow transplantation unit in Italy to reduce VRE carriage.[33] The VRE carriage rates 3 months after the introduction of the diet (3·6% [five of 137]) were significantly lower than those 3 months before introduction (16% [22 of 137]). This finding from a single-centre study warrants further validation through RCTs.

In summary, although the number of prospective human studies on this aspect is low, dietary adjustments aimed at enhancing bacterial diversity or specific metabolic needs could serve as a complementary approach to reducing AMR. Combining these strategies with other microbiota-targeted therapies appears particularly promising.

Probiotics, prebiotics, and defined bacterial consortia

Probiotics, defined as live microorganisms that confer health benefits to the host when administered in adequate amounts, represent another avenue for microbiome modulation.[34] *Lactobacillus*, a common genus contained in several probiotics, is associated with a reduced rate of MDRO acquisition in hospitalised patients.[35] Prebiotics are non-digestible dietary fibres that selectively stimulate the

growth and activity of beneficial bacteria in the gut.[34] By providing substrates for beneficial microbes, prebiotics promote a healthy microbiome composition and function, thereby reducing the risk of AMR.

The effectiveness of probiotics and prebiotics in eradicating MDROs remains a subject of ongoing research.[36] Findings from a systematic review of 29 RCTs involving 2871 individuals who underwent either probiotics or placebo treatment to decolonise AMR pathogens indicated that the persistence of pathogenic bacteria after treatment with probiotics was 22%, whereas that after treatment with placebo was 30·8%. The pooled odds ratio was 0·59 (95% CI 0·43–0·81), favouring probiotics with moderate certainty (p=0·0001). The type of probiotics (p<0·018) and pathogens (p<0·02) significantly affects the outcome of decolonisation, with higher efficacy against Enterobacterales than against VRE.[36] However, a limitation of this systematic review was that aggregating many different bacterial strains and pathogens, including *C difficile*, might have enhanced the perceived efficacy of the probiotics.

Several RCTs have helped to confirm reductions in MDRO carriage rates (including those for VRE and ESBL-producing organisms) in individuals who received prebiotic supplementation over those in the controls.[37] Engineered probiotics, such as strains of *Escherichia coli* producing antimicrobial peptides, have shown potential against multiple pathogens, although most of the evidence was obtained in mouse models.[38]

Thus, probiotics and prebiotics can be considered to contribute to pathogen decolonisation with moderate certainty, but further evidence is needed to identify the exact strains responsible and how they could effectively help to reduce MDRO colonisation in individuals.[39–41]

Consortia, composed of multiple bacterial strains with complementary antimicrobial activities, can effectively target and disrupt MDRO biofilms and inhibit their growth.[42] In 2023, Medlock and colleagues[43] reported that VE707, a defined bacterial consortium of 94 live biotherapeutic products, resulted in a greater than 3-$\log_{10}$ reduction (p=0·002) in the colonisation of *K pneumoniae* and *E coli* in a mouse model, thus suggesting the potential for application in humans.

Honda and colleagues isolated and downselected commensal bacterial consortia from healthy human stool samples capable of strongly and specifically suppressing intestinal Enterobacterales in a mouse model.[44] One such consortium, consisting of 18 commensal strains, effectively controlled ecological niches by regulating gluconate availability, thereby re-establishing colonisation resistance and alleviating antibiotic-resistant *Klebsiella*-driven intestinal inflammation in mice.[44] Nutrient competition between bacterial strains is most likely more efficient when highly related species are used; for example, Osbelt and colleagues[42] showed that *Klebsiella oxytoca* reduces gut colonisation of multidrug-resistant *K pneumoniae* strains in antibiotic-treated and gnotobiotic mouse models. Although more research is needed to fully elucidate the mechanisms governing effective competition (including other nutritional dependencies and the role of interspecies cooperation, among others), these findings lay a robust foundation for the development of microbiota-directed therapeutics to suppress MDROs by means of ecological control and direct intragenera competition.

Ultimately, live biotherapeutic products are considered similar to any product intended to prevent or treat diseases and have to be registered as medicinal products to reach the market in the USA and in Europe.[45] In these two continents these regulatory frameworks require harmonisation, such as the formal adoption of WHO guidelines on procedures and data requirements for changes to approved biotherapeutic products by WHO Expert Committee on Biological Standardisation in 2017.[46]

Bacteriophage therapy

Interest in the use of bacteriophages (phages) to eliminate antibiotic-resistant bacteria has re-emerged as a viable approach to combating MDROs.[39] Bacteriophage therapy has shown effectiveness against *K pneumoniae* and multidrug-resistant *Pseudomonas aeruginosa*, without affecting other gut bacteria.[47]

Bacteriophages are viruses that infect and lyse specific bacterial hosts, making them a precise tool for addressing bacterial infections. Ranveer and colleagues showed that phages have the potential to selectively lyse pathogenic bacteria and preserve the native microbiota at the same time,[40] a key advantage over broad-spectrum antibiotics. Despite being a strength, specificity also hampers the broad application of phages. Thus far, although numerous individual case reports have highlighted the potential efficacy of phages in eradicating MDROs, RCTs with defined outcome measures are lacking.[41] Phage therapy faces regulatory hurdles and requires rigorous clinical testing to establish its safety, efficacy, and standardisation. Additionally, the development of phage resistance has not been well studied.

Selective digestive decontamination

Selective digestive decontamination (SDD) has been widely studied for the decolonisation of the digestive tract, most frequently using an oral mixture of colistin and aminoglycoside. A 2024 meta-analysis of five RCTs confirmed short-term benefits for ESBL-E or CRE decolonisation, although the long-term effects after 1 month remain uncertain.[48] Huttner and colleagues showed a high effectiveness of this strategy in their study.[49] However, Lübbert and colleagues observed a rapid emergence of secondary resistance to gentamicin and colistin following SDD in patients with *Klebsiella pneumoniae* carbapenemase (KPC-2)-producing *K pneumoniae*.[50]

Nevertheless, some studies further evaluated the role of SDD in reducing subsequent MDRO infections. In a retrospective non-randomised trial involving 3266 participants, Martínez-Pérez and colleagues showed that the implementation of the SDD protocol in an intensive care unit (ICU) setting reduced the consumption of antibiotics

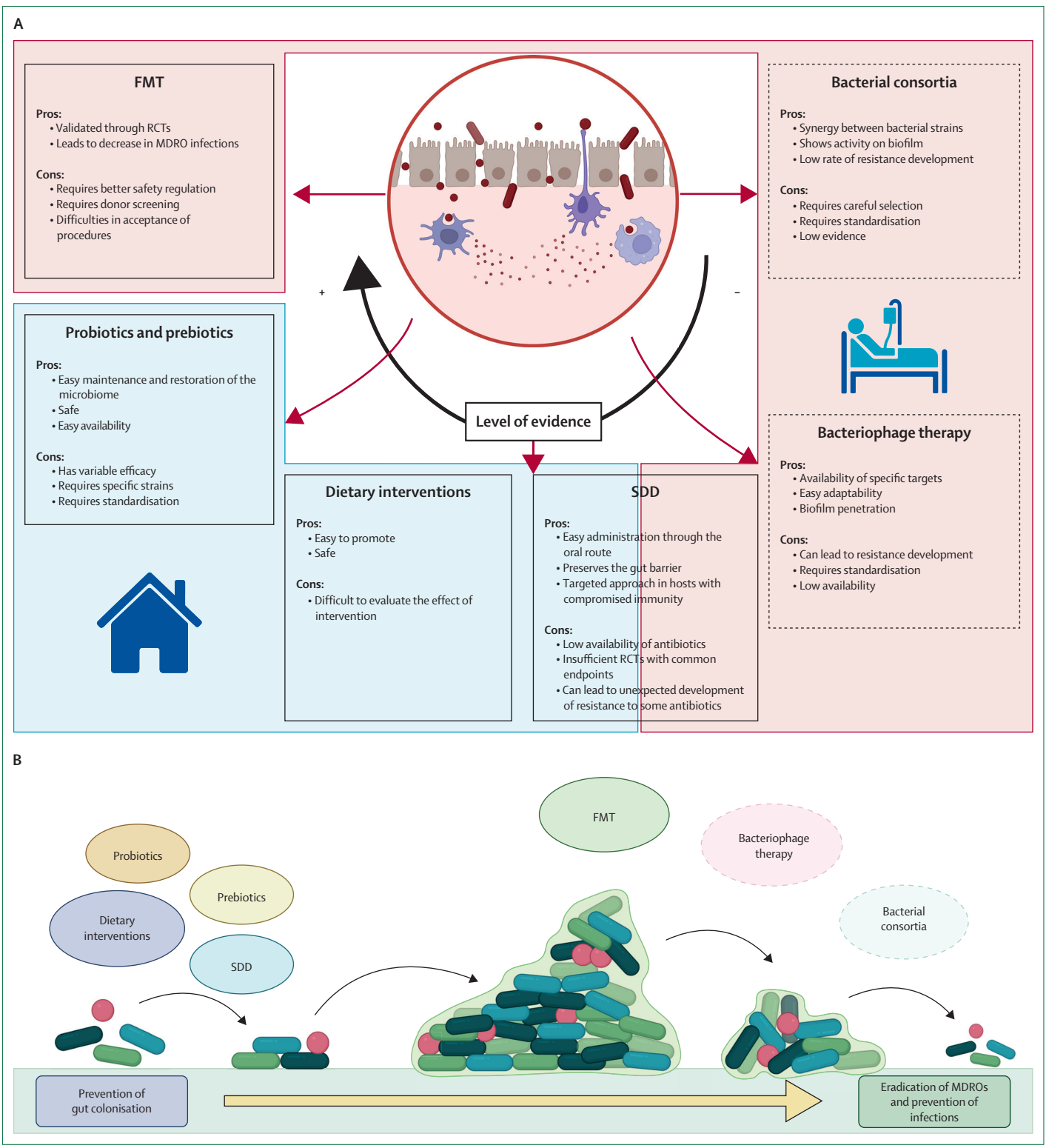

Figure: **Microbiome to control MDROs**

(A) In-hospital and outpatient strategies for targeting the microbiome to control MDROs. Pink squares are in-hospital therapies, and blue squares are outpatient therapies. Arrows indicate the available literature from high (+) to low (–) evidence. (B) Possible strategies for targeting the microbiome to control MDRO colonisation and treat MDRO infections. Biorender.com was used to create the figure. FMT=faecal microbiota transplantation. MDROs=multidrug-resistant organisms. RCTs=randomised clinical trials. SDD=selective digestive decontamination.

	Specific endpoints	Description or focus
Clinical outcomes	Reduction in MDRO carriage or colonisation	Changes in the prevalence or density of MDROs in the gut after interventions
	Infection rates	Incidence of MDRO-related infections (eg, bloodstream infections, urinary tract infections, pneumonia)
	Treatment success	Evaluation of reduced antibiotic use or improved patient outcomes following therapy
	Recurrence rates	Monitoring long-term efficacy in preventing MDRO recolonisation or reinfection
Microbiological endpoints	Diversity and composition of the gut microbiota	Analysis of changes in the microbial diversity and beneficial taxa that inhibit MDROs
	Resistome dynamics	Tracking changes in the abundance and diversity of antibiotic resistance genes in the gut
	Pathogen-specific outcomes	Reductions in specific MDROs, such as ESBL-producing *Escherichia coli*, CRE, or VRE
Microbiome–host interactions	Metabolomic changes	Shifts in gut metabolites (eg, short-chain fatty acids, bile acid derivatives) that influence MDRO growth or virulence
	Immunological responses	Changes in gut immune markers, such as cytokines, mucosal IgA, or T-cell activity
	Microbial interactions	Competitive-exclusion mechanisms or antimicrobial activity of therapeutic microbiota
Safety and tolerability	Adverse events	Monitoring any adverse reactions to microbiome-targeted therapies, including faecal microbiota transplantation or probiotics
Economic and QoL metrics	Cost-effectiveness	Economic effects of microbiome therapies compared with those of traditional antibiotic treatments
	Patient-reported outcomes	Improvements in QoL, reduced number of hospital admissions (ie, for recurrent *Clostridioides difficile* infection)

CRE=carbapenem-resistant Enterobacterales. ESBL=extended-spectrum β-lactamase. MDROs=multidrug-resistant organisms. QoL=quality of life. VRE=vancomycin-resistant enterococci.

Table: **Possible endpoints to assess the effect of microbiome interventions to fight multidrug-resistant organisms**

by 30% (p=0·03), including carbapenems, and decreased colonisation by CPE.[51] In another retrospective study conducted in Spain over 16 years, the bacterial ecology was analysed. The findings revealed that ICUs in Spain without SDD had higher susceptibility rates for *E coli*, *Proteus mirabilis*, and *Enterococcus faecalis* than those with SDD.[52] Similarly, findings from a 2013 meta-analysis also revealed that in an ICU setting, individuals receiving SDD had a lower incidence of colonisation or infection with MDROs than that in non-recipients.[53] A Spanish research team proposed SDD as a strategy to contain an outbreak in a 30-bed medical-surgical ICU that was highly endemic for MDROs.[54] Findings from this study also revealed low rates of colistin-resistant and tobramycin-resistant colonisation, with a non-significant increase in ICU colonisation resistance over 1000 days. In addition, a significant decrease in ventilator-associated pneumonia and bloodstream infections was also reported.

A longitudinal study on the effect of SDD over 21 years in the Netherlands revealed that the incidence rates of MDROs at the ICU level did not increase significantly over time despite an increase in the background resistance rates during the same time period, suggesting a possible benefit of SDD.[55]

Finally, the effectiveness of oral gentamicin in five haematological stem-cell transplant recipients with carbapenem-resistant *K pneumoniae* colonisation was assessed to be 60%, with no resistance detected thereafter, and allowed transplantations with all patients being alive.[56] Similarly, oral gentamicin therapy for gut colonisation with carbapenem-resistant *K pneumoniae* in 14 patients with haematological malignancies presented an effectiveness of 71%, regardless of the use of concomitant systemic antibiotic therapy.[57]

Although SDD might be relevant in specific contexts, such as during outbreaks in hospital units with a high prevalence of MDROs or before a specific intervention in individuals with compromised immunity, increasing the non-susceptibility of CPEs to aminoglycosides poses a substantial challenge. Moreover, one of the main limitations of all these studies is the absence of a common endpoint with a randomised and ideally multicentre clinical trial design to improve generalisability beyond single-centre designs and account for the natural evolution of resistance over time.

Challenges and future directions

Currently, opportunities to target the microbiome for eradicating colonisation and reducing the incidence of MDRO infections are increasing (figure). While several RCTs have been or are being conducted for some of these interventions, evidence for others is still scant, and none have yet received approval for clinical practice. This gap highlights the crucial need for future research to define a potential multi-step approach to combating MDROs.

The development and implementation of microbiome-based interventions face several challenges, including regulatory considerations, which are paramount to ensure safety and ethical conduct. Additionally, implementing dietary interventions and prebiotic and probiotic studies is challenging due to the heterogeneous nature of the interventions and the poor financial interest in them. Globally, these dietary interventions have the highest potential to alleviate the burden of AMR and MDROs, and, in addition, could be more acceptable to the affected individuals, a factor crucial for the success of an intervention.

Further research is required to optimise treatment protocols for specific MDROs, including the evaluation of variable dosing schemes, previous or concomitant treatments, and their long-term effects on microbial ecology and host health. To guide future research on leveraging the gut microbiome to combat MDROs, a focus on clinical,

microbiological, immunological, and economic endpoints is essential (table).

The ecological principles governing microbiota assembly post-FMT remain poorly understood. Although donor strain engraftment is enhanced by antibiotic pretreatment and bowel lavage, the process is also influenced by the alpha-diversity of the microbiota in both the donor and the recipient. Evidence suggests that donor strain engraftment after FMT is strongly dependent on microbiota composition and dysbiosis in the recipient. This finding highlights the potential for developing personalised FMT applications for the treatment of microbiota-associated pathologies within the framework of precision medicine.[58]

We suggest that the outcomes of MDRO decolonisation and infection should be analysed separately, particularly since the outcomes of MDRO infection may be more achievable and clinically significant. Additionally, the combined use of various microbiome-targeted interventions, from prevention to treatment and outpatient to in-hospital care, could yield better results than individual treatments, particularly in hosts with compromised immunity. Preventive strategies aimed at reducing the gut MDRO burden may subsequently reduce the risk of invasive MDRO infections (figure).

Conclusions

The gut microbiome represents a promising frontier in efforts to combat colonisation and infections caused by MDROs. Innovative interventions such as FMT, probiotics, prebiotics, phage therapy, SDD, and bacterial consortia offer potential solutions to the crisis posed by AMR. However, significant challenges remain, including regulatory hurdles, acceptance by affected individuals, and the need for further research to substantiate these approaches. Priority should be given to fostering collaboration, driving innovation, and adopting evidence-based practices to harness the potential of the microbiome to combat AMR and protect the health and wellbeing of current and future generations.

Contributors

SC and BD conceived the study. SC, BD, BM, and LMB drafted the paper. SC, BD, LMB, EK, and BM performed the literature review. SC, BD, BM, EK, and NB edited and revised the paper. All authors agree to be accountable for the integrity and accuracy of the work.

Declaration of interests

We declare no competing interests.

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References

1 Pettigrew MM, Johnson JK, Harris AD. The human microbiota: novel targets for hospital-acquired infections and antibiotic resistance. *Ann Epidemiol* 2016; **26:** 342–47.

2 Merrick B, Sergaki C, Edwards L, et al. Modulation of the gut microbiota to control antimicrobial resistance (AMR)-a narrative review with a focus on faecal microbiota transplantation (FMT). *Infect Dis Rep* 2023; **15:** 238–54.

3 Vliex LMM, Penders J, Nauta A, Zoetendal EG, Blaak EE. The individual response to antibiotics and diet — insights into gut microbial resilience and host metabolism. *Nat Rev Endocrinol* 2024; **20:** 387–98.

4 WHO. WHO bacterial priority pathogens list, 2024: Bacterial pathogens of public health importance to guide research, development and strategies to prevent and control antimicrobial resistance. May 17, 2024. https://www.who.int/publications/i/item/9789240093461 (accessed July 17, 2024).

5 Tacconelli E, Mazzaferri F, de Smet AM, et al. ESCMID-EUCIC clinical guidelines on decolonization of multidrug-resistant Gram-negative bacteria carriers. *Clin Microbiol Infect* 2019; **25:** 807–17.

6 Millan B, Park H, Hotte N, et al. Fecal microbial transplants reduce antibiotic-resistant genes in patients with recurrent *Clostridium difficile* infection. *Clin Infect Dis* 2016; **62:** 1479–86.

7 Singh R, de Groot PF, Geerlings SE, et al. Fecal microbiota transplantation against intestinal colonization by extended-spectrum beta-lactamase-producing Enterobacteriaceae: a proof of principle study. *BMC Res Notes* 2018; **11:** 190.

8 Dinh A, Fessi H, Duran C, et al. Clearance of carbapenem-resistant Enterobacteriaceae vs vancomycin-resistant Enterococci carriage after fecal microbiota transplant: a prospective comparative study. *J Hosp Infect* 2018; **99:** 481–86.

9 Davido B, Batista R, Fessi H, et al. Fecal microbiota transplantation to eradicate vancomycin-resistant enterococci colonization in case of an outbreak. *Med Mal Infect* 2019; **49:** 214–18.

10 Seong H, Lee SK, Cheon JH, et al. Fecal microbiota transplantation for multidrug-resistant organism: efficacy and response prediction. *J Infect* 2020; **81:** 719–25.

11 Hyun J, Lee SK, Cheon JH, et al. Faecal microbiota transplantation reduces amounts of antibiotic resistance genes in patients with multidrug-resistant organisms. *Antimicrob Resist Infect Control* 2022; **11:** 20.

12 Nooij S, Vendrik KEW, Zwittink RD, et al. Long-term beneficial effect of faecal microbiota transplantation on colonisation of multidrug-resistant bacteria and resistome abundance in patients with recurrent *Clostridioides difficile* infection. *Genome Med* 2024; **16:** 37.

13 Davido B, Moussiegt A, Dinh A, et al. Germs of thrones - spontaneous decolonization of carbapenem-resistant Enterobacteriaceae (CRE) and vancomycin-resistant Enterococci (VRE) in Western Europe: is this myth or reality? *Antimicrob Resist Infect Control* 2018; **7:** 100.

14 Bar-Yoseph H, Hussein K, Braun E, Paul M. Natural history and decolonization strategies for ESBL/carbapenem-resistant Enterobacteriaceae carriage: systematic review and meta-analysis. *J Antimicrob Chemother* 2016; **71:** 2729–39.

15 Huttner BD, de Lastours V, Wassenberg M, et al. A 5-day course of oral antibiotics followed by faecal transplantation to eradicate carriage of multidrug-resistant Enterobacteriaceae: a randomized clinical trial. *Clin Microbiol Infect* 2019; **25:** 830–38.

16 Woodworth MH, Conrad RE, Haldopoulos M, et al. Fecal microbiota transplantation promotes reduction of antimicrobial resistance by strain replacement. *Sci Transl Med* 2023; **15:** eabo2750.

17 Ghani R, Mullish BH, McDonald JAK, et al. Disease prevention not decolonization: a model for fecal microbiota transplantation in patients colonized with multidrug-resistant organisms. *Clin Infect Dis* 2021; **72:** 1444–47.

18 Davido B, Watson AR, de Truchis P, et al. Bacterial diversity and specific taxa are associated with decolonization of carbapenemase-producing Enterobacterales after fecal microbiota transplantation. *J Infect* 2024; **89:** 106216.

19 Merrick B, Allen L, Zain NMM, et al. Regulation, risk and safety of faecal microbiota transplant. *Infect Prev Pract* 2020; **2:** 100069.

20 Benech N, Cassir N, Alric L, et al. Impact of clinical and pharmacological parameters on faecal microbiota transplantation outcome in *Clostridioides difficile* infections: results of a 5-year French national survey. *Aliment Pharmacol Ther* 2025; **61:** 159–67.

21 Davido B, Batista R, Dinh A, et al. Fifty shades of graft: how to improve the efficacy of faecal microbiota transplantation for decolonization of antibiotic-resistant bacteria. *Int J Antimicrob Agents* 2019; **53:** 553–56.

22 Zmora N, Suez J, Elinav E. You are what you eat: diet, health and the gut microbiota. *Nat Rev Gastroenterol Hepatol* 2019; **16:** 35–56.

23 Oliver A, Xue Z, Villanueva YT, et al. Association of diet and antimicrobial resistance in healthy U.S. adults. *mBio* 2022; **13:** e0010122.

24 Chen M, Zhao Z, Meng H, Yu S. The antibiotic activity and mechanisms of sugar beet (*Beta vulgaris*) molasses polyphenols against selected food-borne pathogens. *LWT-Food Sci Technol* 2017; **82:** 354–60.

25 David LA, Maurice CF, Carmody RN, et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature* 2014; **505:** 559–63.

26 Phillips I, Casewell M, Cox T, et al. Does the use of antibiotics in food animals pose a risk to human health? A critical review of published data. *J Antimicrob Chemother* 2004; **53:** 28–52.

27 Stege PB, Hordijk J, Shetty SA, et al. Impact of long-term dietary habits on the human gut resistome in the Dutch population. *Sci Rep* 2022; **12:** 1892.

28 Meijs AP, Gijsbers EF, Hengeveld PD, et al. Do vegetarians less frequently carry ESBL/pAmpC-producing *Escherichia coli/Klebsiella pneumoniae* compared with non-vegetarians? *J Antimicrob Chemother* 2020; **75:** 550–58.

29 Wastyk HC, Fragiadakis GK, Perelman D, et al. Gut-microbiota-targeted diets modulate human immune status. *Cell* 2021; **184:** 4137–53.e14.

30 Ng KM, Aranda-Díaz A, Tropini C, et al. Recovery of the gut microbiota after antibiotics depends on host diet, community context, and environmental reservoirs. *Cell Host Microbe* 2019; **26:** 650–65.e4.

31 Eggers S, Malecki KM, Peppard P, et al. Wisconsin microbiome study, a cross-sectional investigation of dietary fibre, microbiome composition and antibiotic-resistant organisms: rationale and methods. *BMJ Open* 2018; **8:** e019450.

32 Stein-Thoeringer CK, Nichols KB, Lazrak A, et al. Lactose drives *Enterococcus* expansion to promote graft-versus-host disease. *Science* 2019; **366:** 1143–49.

33 Morello E, Roversi S, Brambilla G, et al. Nutritional strategies to improve VRE control. *Transplant Cell Ther* 2024; **30:** 548.e1–4.

34 Rastall RA, Gibson GR. Recent developments in prebiotics to selectively impact beneficial microbes and promote intestinal health. *Curr Opin Biotechnol* 2015; **32:** 42–46.

35 Araos R, Tai AK, Snyder GM, Blaser MJ, D'Agata EMC. Predominance of *Lactobacillus* spp among patients who do not acquire multidrug-resistant organisms. *Clin Infect Dis* 2016; **63:** 937–43.

36 Rahman MN, Barua N, Tin MCF, Dharmaratne P, Wong SH, Ip M. The use of probiotics and prebiotics in decolonizing pathogenic bacteria from the gut; a systematic review and meta-analysis of clinical outcomes. *Gut Microbes* 2024; **16:** 2356279.

37 Newman AM, Arshad M. The role of probiotics, prebiotics and synbiotics in combating multidrug-resistant organisms. *Clin Ther* 2020; **42:** 1637–48.

38 Li X, Song L, Zhu S, et al. Two strains of lactobacilli effectively decrease the colonization of VRE in a mouse model. *Front Cell Infect Microbiol* 2019; **9:** 6.

39 Aslam S, Schooley RT. What's old is new again: bacteriophage therapy in the 21st century. *Antimicrob Agents Chemother* 2019; **64:** e01987-19.

40 Ranveer SA, Dasriya V, Ahmad MF, et al. Positive and negative aspects of bacteriophages and their immense role in the food chain. *NPJ Sci Food* 2024; **8:** 1.

41 El Haddad L, Harb CP, Gebara MA, Stibich MA, Chemaly RF. A systematic and critical review of bacteriophage therapy against multidrug-resistant ESKAPE organisms in humans. *Clin Infect Dis* 2019; **69:** 167–78.

42 Osbelt L, Wende M, Almási É, et al. *Klebsiella oxytoca* causes colonization resistance against multidrug-resistant *K pneumoniae* in the gut via cooperative carbohydrate competition. *Cell Host Microbe* 2021; **29:** 1663–79.e7.

43 Medlock G, Felix C, Alsharif W, et al. 2521. VE707, a defined live biotherapeutic product for prevention of infection by multidrug-resistant Gram-negative bacteria. *Open Forum Infect Dis* 2023; **10:** ofad500.2139.

44 Honda K, Furuichi M, Kawaguchi T, et al. Rationally-defined microbial consortia suppress multidrug-resistant proinflammatory Enterobacteriaceae via ecological control. *Res Sq* 2023; published online Oct 23. https://doi.org/10.21203/rs.3.rs-3462622/v1 (preprint).

45 Cordaillat-Simmons M, Rouanet A, Pot B. Live biotherapeutic products: the importance of a defined regulatory framework. *Exp Mol Med* 2020; **52:** 1397–406.

46 Wadhwa M, Kang HN, Hamel H, Jivapaisarnpong T. WHO informal consultation on development of guidelines on procedures and data requirements for changes to approved biotherapeutic products, Seoul, Republic of Korea, 27–28 April 2017. *Biologicals* 2018; **52:** 83–91.

47 Bonnet M, Eckert C, Tournebize R. Decolonization of asymptomatic carriage of multi-drug resistant bacteria by bacteriophages? *Front Microbiol* 2023; **14:** 1266416.

48 Zhang HJ, Wang HW, Tian FY, et al. Decolonization strategies for ESBL-producing or carbapenem-resistant Enterobacterales carriage: a systematic review and meta-analysis. *Sci Rep* 2024; **14:** 24349.

49 Huttner B, Haustein T, Uçkay I, et al. Decolonization of intestinal carriage of extended-spectrum β-lactamase-producing Enterobacteriaceae with oral colistin and neomycin: a randomized, double-blind, placebo-controlled trial. *J Antimicrob Chemother* 2013; **68:** 2375–82.

50 Lübbert C, Faucheux S, Becker-Rux D, et al. Rapid emergence of secondary resistance to gentamicin and colistin following selective digestive decontamination in patients with KPC-2-producing *Klebsiella pneumoniae*: a single-centre experience. *Int J Antimicrob Agents* 2013; **42:** 565–70.

51 Martínez-Pérez M, Fernández-Fernández R, Morón R, et al. Selective digestive decontamination: a comprehensive approach to reducing nosocomial infections and antimicrobial resistance in the ICU. *J Clin Med* 2024; **13:** 6482.

52 Lloréns-Villar Y, Tusell F, Canut A, et al. Antibiotic susceptibility trend before and after long-term use of selective digestive decontamination: a 16 year ecological study. *J Antimicrob Chemother* 2019; **74:** 2289–94.

53 Daneman N, Sarwar S, Fowler RA, Cuthbertson BH. Effect of selective decontamination on antimicrobial resistance in intensive care units: a systematic review and meta-analysis. *Lancet Infect Dis* 2013; **13:** 328–41.

54 Sánchez-Ramírez C, Hípola-Escalada S, Cabrera-Santana M, et al. Long-term use of selective digestive decontamination in an ICU highly endemic for bacterial resistance. *Crit Care* 2018; **22:** 141.

55 Buitinck S, Jansen R, Rijkenberg S, et al. The ecological effects of selective decontamination of the digestive tract (SDD) on antimicrobial resistance: a 21-year longitudinal single-centre study. *Crit Care* 2019; **23:** 208.

56 De Rosa FG, Corcione S, Raviolo S, Bruno B, Busca A. Management of carbapenem-resistant *K. pneumoniae* in allogenic stem cell transplant recipients: the Turin bundle. *New Microbiol* 2017; **40:** 143–45.

57 Lambelet P, Tascini C, Fortunato S, et al. Oral gentamicin therapy for carbapenem-resistant *Klebsiella pneumoniae* gut colonization in hematologic patients: a single center experience. *New Microbiol* 2017; **40:** 161–64.

58 Podlesny D, Durdevic M, Paramsothy S, et al. Identification of clinical and ecological determinants of strain engraftment after fecal microbiota transplantation using metagenomics. *Cell Rep Med* 2022; **3:** 100711.