Rapid projects support government departments to understand the scientific evidence underpinning a policy issue or area by convening academic, industry and government experts at a single roundtable. These summary meeting notes seek to provide accessible science advice for policymakers. They represent the combined views of roundtable participants at the time of the discussion and are not statements of government policy.

"What do we already know about microbiome manipulation via diet, prebiotic and probiotic, and other interventions, and what are the research gaps?"
Meeting note from roundtable chaired by Robin May, Chief Scientific Adviser at the Food Standards Agency, facilitated by the Government Office for Science
16 April 2024, 15:00-16:30

Key points

- The gut microbiome is highly complex and varies considerably among individuals. Rather than seeking to define a "healthy" or "unhealthy" gut microbiome, research should focus on profiling the baseline gut microbiome to better understand the impacts of dietary and other interventions targeting the gut microbiome (e.g., probiotics, prebiotics, microbial transplants).
- Prebiotics and probiotics may have different and sometimes minimal effects on the gut microbiome due to variability in the microbiome, differences in diet and other characteristics among individuals. There are also variations in biological responses to probiotics among individuals. Actions should be taken to increase public/consumer awareness of these considerations so they can make more informed decisions.
- There is public interest in fermented foods and their influence on the microbiome, but the available scientific literature is sparse. There is currently a lack of evidence on the effectiveness of fermented foods for positive health impacts, although evidence continues to emerge, but there is increasing evidence of fermented foods containing antibiotic resistant pathogens.
- When administered responsibly, faecal microbiota transplantation (FMT) has been shown to help reinstate diversity in the gut microbiome. Use of FMT is regulated in the UK but more research is needed to increase its range of applications.
- Measuring metabolite production and other biomarkers is useful in understanding changes to the gut microbiome over time, but taking reliable measurements is difficult using current methods due to the nature of the samples and limitations in methodologies.
- Work is needed to establish clear clinical research regulations for gut microbiome research, particularly for dietary, probiotic and prebiotic interventions. Ethics committees should work with researchers to enable easier implementation of clinical studies for prebiotics and probiotics.

Current understanding of microbiome composition, function and metabolic activity

1. The microbiome refers to the community of microorganisms, their metabolites (small biological molecules that are products of chemical reactions within the body) and the environment they inhabit. The human body has several microbiomes including the skin, oral and gut microbiomes. There are differences in composition (what and how many species are present) and function between different microbiomes, as well as within a specific microbiome (e.g., variations exist in different sites of the gut microbiome, such as the small and large intestine). This note will specifically focus on the gut microbiome and interventions that influence it.

2. It is difficult to define a “healthy” or "unhealthy” gut microbiome in terms of composition. It is known that a "healthy" microbiome should be well balanced (both in terms of diversity and co-existence of species) and is associated with the presence of specific bacteria such as *Bifidobacterium* and *Akkermansia*.
3. Bacteria that are considered to be beneficial can also have negative impacts on health. For example, high amounts of *Akkermansia* have been associated with thinning of the intestinal wall (Qu, et al., 2023) and kidney disease (Gleeson, et al., 2024). *Bifidobacterium*, found in probiotic products, is related to a few rare cases of sepsis in infants (Kulkarni, et al., 2022). However, these rare negative impacts should be weighed against the many positive cases of improved health and reduced disease.
4. More important is understanding the microbiome in the context of function, its interaction with the body and its processes, and measurements of microbial activity (e.g., bacterial enzyme activity and production of metabolites). There is a need for more basic research to understand which microbes and which activated mechanisms could be beneficial and have functional significance to allow for targeted interventions.
5. High microbiome diversity is one important positive indicator of gut health in adults; the greater the range of different species present in the gut microbiome, the more functions they will be able to perform and the more resilient the gut is to pathogens.
6. Recently, intense public interest in the gut microbiome has driven significant media activity, such as documentaries that highlight its importance. There should be a concerted effort to raise awareness of the microbiome and the interventions that affect it, both among the general public and in other sectors, such as healthcare. This will require collaboration involving researchers, regulators, ethics committees and patient groups, among others.

Current interventions for gut microbiome manipulation

7. There are many ways by which the gut microbiome can be altered, including by prebiotics and probiotics, antibiotics, hormone changes (e.g., during menopause), pregnancy, changes in diet, diarrhoea-inducing illnesses, and interventions such as FMT.
8. Probiotics can be live biotherapeutic products (a biological product containing live microorganisms) or food products that contain live microorganisms, such as bacteria (Hill et al., 2014), while prebiotics are foods that “feed” specific bacteria within the microbiome (Gibson et al., 2017). They are both used to confer a health benefit to the body, but probiotics and prebiotics are not “one-size fits all interventions: the same probiotic/prebiotic may have different effects on the microbiome and general health due to gut microbiome variability, differences in diet and other characteristics among individuals. Actions should be taken to increase public/consumer awareness of these issues so they can make more informed decisions.
9. Modifications in diet will induce changes in the gut microbiome (David et al., 2013). These changes are dynamic. For example, eating more fermentable fibre(s) can result in substantial alterations in the gut microbiome, but these can be reversed once a previous diet is resumed. These changes can also vary according to the complexity of dietary products; one food supplement may make a small change to a small number of specific bacterial species, while dietary modifications, involving a range of different foods, can change global microbiome composition significantly.
10. Geographical location (nationally and internationally) can influence diet and therefore the gut microbiome. The African Microbiome Institute (AMI) has found different concentrations of metabolites in food in rural and urban areas, with greater variety of metabolites in rural areas (Ramaboli, et al., 2024).
11. Age can also influence diet. For example, babies and infants have different (mostly homogenous) diets to adults and do not have as much free choice regarding diet, which

results in them having less diverse gut microbiomes. The low diversity of the gut microbiome in babies/infants may allow for easier microbiome manipulation. This could be beneficial for interventions such as probiotics, which have been found to have a high level of therapeutic potential in infants, specifically to prevent necrotising enterocolitis (NEC); 40% of neonatal intensive care units in the UK use probiotics as a cheap and easy treatment for illness (Patel, et al., 2023). Probiotic products given to babies should be regulated and decisions to administer should be strictly guided by medical professionals.

12. There is wide public interest in fermented foods (e.g., kimchi, kefir and kombucha) and their influence on the microbiome. However, the scientific literature on fermented foods is sparse. There is currently very little evidence that bacteria, or their metabolites, from fermented foods successfully transfer and integrate within the gut microbiome for positive health impacts (Dimidi, et al., 2019), although some evidence of positive health impacts is emerging (Taylor et al., 2020). At the same time, home-made fermented foods carry safety risks if not produced under appropriate conditions and can, for example, potentially introduce drug-resistant pathogens (Li, et al., 2023).
13. FMT involves introducing donor faecal matter into the intestinal tract of a recipient to directly change their gut microbial composition, with the aim of achieving health benefits (Gupta, et al., 2016). When administered responsibly, FMT has been shown to help to reinstate diversity in the gut microbiome. There are US, UK, and newly revised EU guidelines to increase the safety and quality of FMT procedures (European Commission, 2024). Use of FMT in the UK is currently limited to *C. difficile* infection cases which have proven unresponsive to antibiotics, and to ulcerative colitis cases. There are ongoing clinical trials in the UK using FMT to treat liver disease, inflammatory bowel disease, inflammatory bowel syndrome and as part of bone marrow transplants. More research is needed before FMT can be approved for other medical conditions.

Challenges and advancements in measuring/analysing the microbiome

14. There is currently a lack of consistency in microbiome analysis, making it difficult to compare studies and limiting the validity of claims. There is a need for standardisation and regulation of microbiome analysis methods. Furthermore, the majority of microbiome data is based on people from the US and other western countries and so does not provide a global population perspective. Study results cannot be generalised between populations due to variations in genetics, diet and environment.
15. Understanding the role of the baseline gut microbiome (i.e. microorganisms that are consistently found within the normal gut microbiome) is important, and before a study is conducted, the baseline microbiome should be considered. Investment in fundamental microbiome science, especially to understand the baseline microbiome, is needed (Shalon, et al., 2023; Maldonado-Gómez, et al. 2016).
16. Response to dietary, prebiotic and probiotic interventions are dependent on this baseline microbiome. For example, people who habitually consume fibre may not see a significant effect on the microbiome after taking prebiotics, because their baseline microbiome is different to people who do not routinely consume significant quantities of dietary fibre.
17. Diet is important in gut microbiome research but is very rarely or inconsistently measured. Controlling and accurately recording the diet of people involved in any trials related to the gut microbiome is important to improve the validity and reliability of studies.
18. One way to measure the microbiome is to identify and quantify specific biomarkers (any biological molecule that acts as a sign of a normal body process or disease), such as metabolites, but this is difficult to do accurately and consistently across studies. Furthermore, there are challenges in understanding how to monitor and measure the

longitudinal nature of changes within the gut microbiome over time to identify specific biomarkers.

19. There are methods for quantifying the production of metabolites, including short chain fatty acids (SCFAs), which have been identified as being beneficial for gut health. However, these are used in many host processes, so measuring these metabolites from stool samples may not provide a fully accurate representation of gut microbiome activity. It is important to measure the gut microbiome and its metabolites using samples that can correlate well with the gut microbiome and can be measured easily. More research is needed on identification of biomarkers relating to the gut microbiome.
20. Methods of retrieving accurate samples from the gut microbiome need improving. If species groups are missing from a microbiome sample, it will affect study results. Smart capsules are being developed for accurate, site-specific sampling and to address the limitations of stool samples (Shalon, et al. 2023). They have the potential to provide a more accurate picture of the gut microbiome.
21. Animal models, such as mice, have been used to understand the impacts of gut microbiome interventions. However, there are considerable physiological differences among species of mice as well as between mice and humans, making it difficult to infer relevance to humans. (Walter, et al. 2020). Animal studies are also difficult to conduct and expensive.
22. Work should be undertaken to establish clear regulation of gut microbiome research, particularly for dietary, probiotic and prebiotic interventions. Ethics committees should collaborate with researchers to enable easier implementation of clinical studies for pre-/pro-biotics.

Attendees

Robin May (Chair; Chief Scientific Adviser, Food Standards Agency), Anisha Wijeyesekera (University of Reading), Chrysi Sergaki (MHRA), Christopher Stewart (Newcastle University), Claire Pearson (University of Oxford), Gabriela Juarez Martinez (Innovate UK Business Connect), Julian Marchesi (Imperial College London), Julie Thompson (Guts UK), Kevin Whelan (King's College London), Lindsay Hall (University of Birmingham), Lynsey Howard (EnteroBiotix), Peter Cotgreave (Microbiology Society), Stephen O'Keefe (University of Pittsburgh & African Microbiome Institute; Stellenbosch University), Tariq Iqbal (University of Birmingham), Trevor Lawley (Wellcome Sanger Institute).

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