MICROBIOTA

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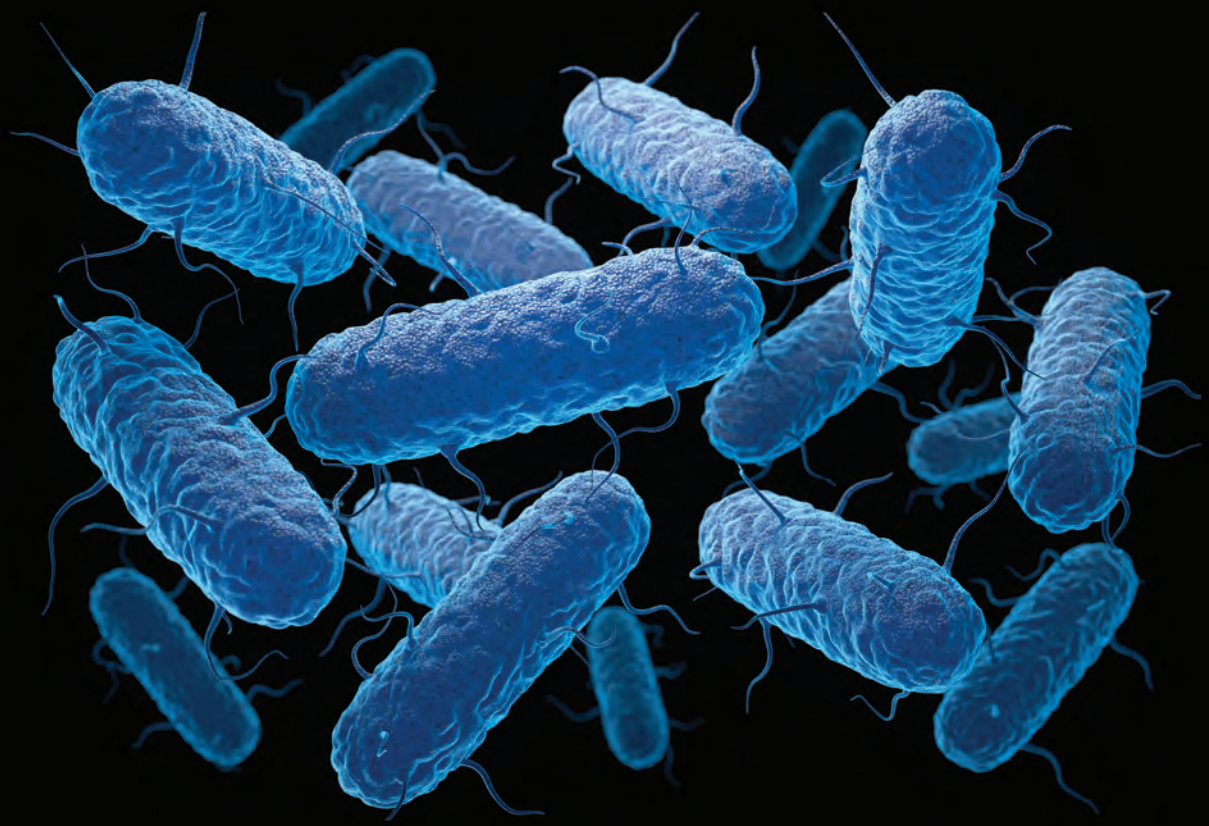

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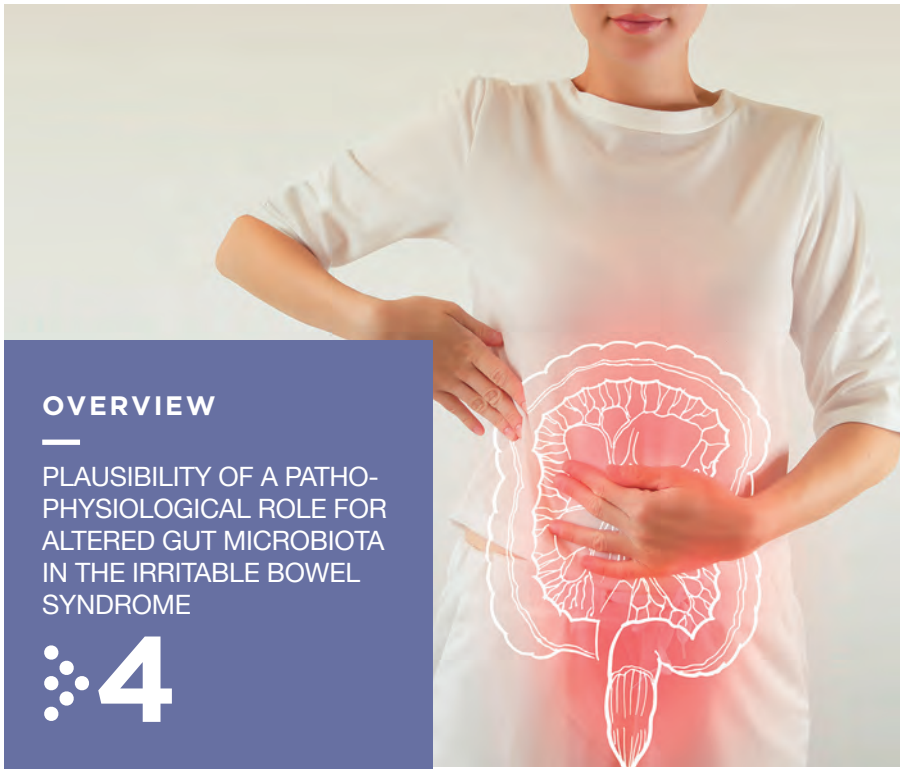
SUMMARY



OVERVIEW

PLAUSIBILITY OF A PATHO-PHYSIOLOGICAL ROLE FOR ALTERED GUT MICROBIOTA IN THE IRRITABLE BOWEL SYNDROME

4

COMMENTED ARTICLE

ADULTS' SECTION

CHILDREN'S SECTION

8

MICROBIOTA & COVID-19

CONGRESS REVIEWS

12

PRESS REVIEW

16

NEWS

BIOCODEX MICROBIOTA INSTITUTE

19

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> **“ RECENTLY PUBLISHED STUDIES HAVE SHED NEW LIGHT ON HOW THE GUT MICROBIOTA MAY BE AFFECTED BY THE VIRUS. BUT TO DATE, NO STUDY HAS EXAMINED THE ROLE OF THE GUT MICROBIOTA ON THE EFFICACY OF THE SARS-COV-2 VACCINE. ”**

Dear readers,

Every day we learn more about the central role that the different microbiota play in our health. Mechanisms of action, links between dysbiosis and certain pathologies, the preventive role of the microbiota, interaction and connection between the different microbiota in our body, synergy of action between the microbiota and certain drugs... Not a week goes by without a new study describing the importance of the microbiota. And the pace has even accelerated with the pandemic. Recently published studies have shed new light on how the gut microbiota may be affected by the virus (see Microbiota 11, 12 and 13). However, to date, no study has examined the role of the gut microbiota on the efficacy of the SARS-CoV-2 vaccine.

It is well known that vaccination serves to activate the specific response of the immune system. There is even a correlation between the immune response to vaccination and the composition of the intestinal microbiota. This immune response varies from one individual to another (state of health, chronic pathologies, age, stress, etc.). But some grey areas remain. What makes this response vary? What exact role does the gut microbiota play? Genelle Healey’s article in this issue gradually lifts the veil on the factors that can influence the vaccine response. According to the author, “it is possible that dysbiosis of the gut microbiome caused by host factors may be involved in the different vaccine responses observed”. The author goes even further, «certain bacterial profiles of the gut microbiota (i.e., higher abundance of Actinobacteria, Clostridium cluster XI and Proteobacteria) are associated with a better vaccine response against certain viral diseases such as HIV, influenza and rotavirus.

It is now an undisputed fact that vaccines are the main hope for controlling SARS-CoV-2, but the heterogeneity of vaccine responses may compromise the fight against COVID-19. What if the gut microbiota were to become the best ally of vaccination? To be continued...

In the meantime, enjoy your reading.

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OVERVIEW

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PLAUSIBILITY OF A PATHOPHYSIOLOGICAL ROLE FOR ALTERED GUT MICROBIOTA IN THE IRRITABLE BOWEL SYNDROME

The irritable bowel syndrome (IBS) is a common functional bowel disorder characterized by abdominal pain, which is associated with changes in stool frequency and/or stool consistency. While not established yet, the pathogenesis and a multitude of putative pathophysiological mechanisms have been proposed, including: disordered motility, visceral hypersensitivity, low-grade inflammation, altered microbiota, immune activation, adverse reactions to foods and central nervous system dysfunction, etc. In 2017, five putative criteria for mechanisms in functional gastrointestinal disorders were published in *Gut*. Here we discuss to which extent altered gut microbiota fulfills these plausibility criteria in the context of IBS and review the available literature on the subject.

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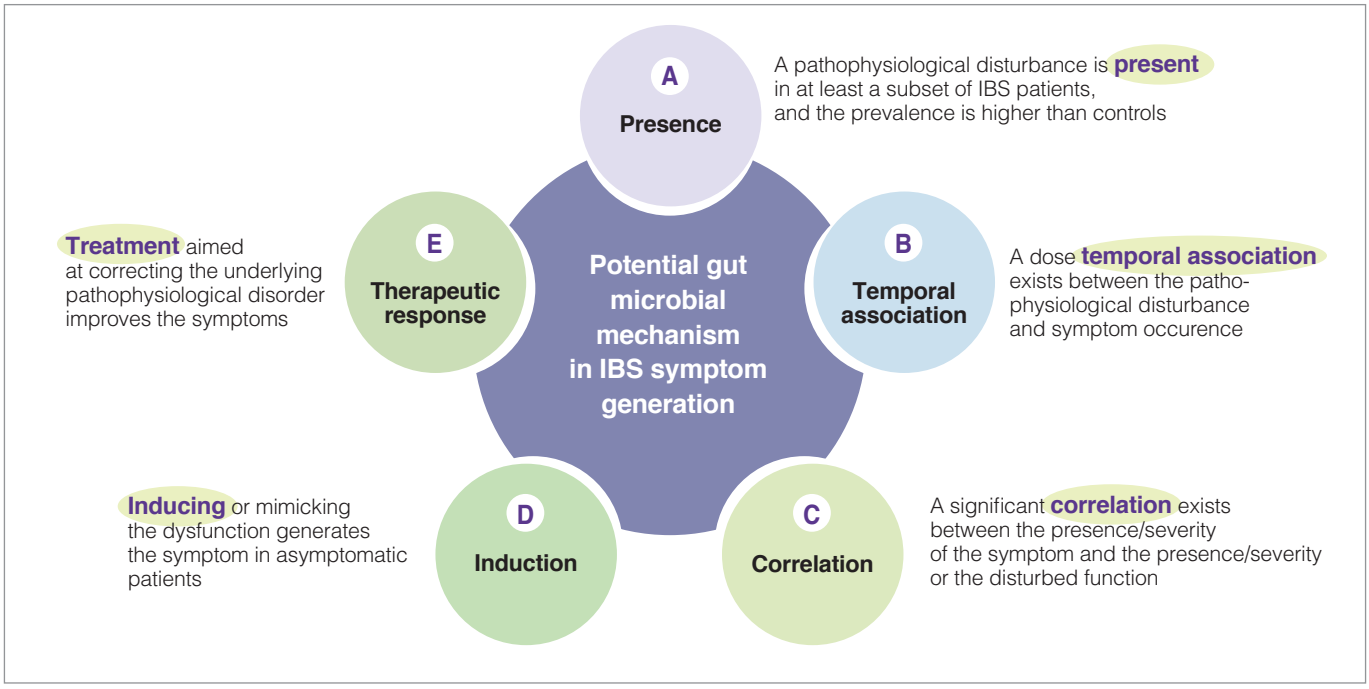
INTRODUCTION

The most common functional bowel disorder, the irritable bowel syndrome (IBS), is characterized by abdominal pain or discomfort and is associated with changes in stool frequency and/or consistency, without identifiable structural or biochemical abnormalities indicating organic disease during routine investigations [1, 2]. Besides abdominal pain, patients also report other gastrointestinal symptoms as bloating, abdominal distention, and flatulence. IBS can be divided into different subtypes, based on the most dominant stool consistency: IBS-C (predominant constipation), IBS-D (predominant diarrhea), and IBS-M (IBS with mixed bowel habits). In terms of pathophysiology, IBS is considered a heterogeneous disorder and different mechanisms have been implicated, including gastrointestinal dysmotility, visceral

▼ FIGURE 1

Plausibility criteria for pathophysiological mechanisms in IBS disorders based on a consensus publication [6], as can be applied for the role of gut microbial mechanisms in the pathogenesis of IBS symptoms.



hypersensitivity, dysfunction of the brain-gut axis and, more recently, changes in bile salt composition and handling, low-grade inflammation, mucosal immune activation, and altered intestinal microbiota [3].

The last decade has seen a major surge in interest in the role of gut microbiota in IBS. The microbial community of the gut exerts a number of functions, including the metabolism of indigestible polysaccharides, the absorption of certain nutrients and ions, the uptake and deposition of dietary lipids, regulation of bile acid metabolism, and the production of vitamins such as folate, biotin and vitamin K [3, 4]. By competing with microbial pathogens, it reinforces the gastrointestinal barrier protection. While interacting intensely with the mucosa, the gut microbiota also affect the immune system and gut-brain signaling of the host [5]. These diverse properties identify gut microbiota as a potential major contributor to the pathophysiology and as an attractive target for therapy in IBS.

Indeed, multiple mechanisms associated with the gut microbial ecosystem, have been identified in IBS pathophysiological studies. They have led to variable arguments and observations to support the relevance of these individual candidate mechanisms. To advance the field there is a need to identify the level of relevance of such putative pathophysiological processes, as this would enhance the knowledge and may prioritize targets for therapeutic innovation or optimization. A few years ago, a group of international experts developed five plausibility criteria for mechanisms in functional gastrointestinal disorders such as IBS [6]. They are based on aspects such as presence, temporal association, correlation between level of impairment and symptom severity, induction in healthy subjects and treatment response (or congruent natural history if no treatment is possible) (**Figure 1**). The following sections will evaluate the putative hypothesis that implicate a change in gut microbiota as a mechanism in IBS symptom generation and presentation (Box). The current knowledge regarding gut microbiota in IBS is summarized, and areas for further research are identified.

PLAUSIBILITY OF A PATHOPHYSIOLOGICAL ROLE FOR GUT MICROBIOTA IN IBS

PRESENCE OF ALTERED GUT MICROBIOTA IN IBS (A)

The first plausibility criterion is that changes in gut microbiota are found in at least a subset of IBS patients [6]. Several studies have investigated the presence and type of alterations of gut microbiota in IBS compared to healthy controls. Pittayanon and colleagues have published in a 2019 a systematic review of 24 studies from 22 publications comparing gut microbiota of patients with IBS (mainly adult) with microbiota of healthy individuals [7]. They concluded that family *Enterobacteriaceae*, family *Lactobacillaceae* and genus *Bacteroides* were increased, whereas *Clostridiales* I, genus *Faecalibacterium*, and genus *Bifidobacterium* were decreased in patients with IBS compared with controls [7]. While these observations make a case for altered microbiota in IBS, there is major heterogeneity in findings between different studies, sample sizes are usually small and most studies occurred in specialized care. Moreover, many studies did not correct statistics for multiple testing and did not consider dietary factors and prior pro- or antibiotic use. Also, no consistent differences were found between IBS stool subtypes [7]. The proportion of IBS patients in whom an altered gut microbiota composition can be identified remains unclear.

TEMPORAL ASSOCIATION, OF ALTERED GUT MICROBIOTA WITH IBS SYMPTOMS (B)

The best evidence for a temporal association between changes in gut microbiota and IBS symptoms can be derived from the clinical entity of post-infection (PI-)IBS [8]. Approximately 10% of patients with infectious enteritis develop PI-IBS with female sex, younger age, psychological distress at the time of the gastroenteritis, and se-

verity of the acute infection as risk factors. Development of PI-IBS is associated with changes in the intestinal microbiome, as well as mucosal alterations (low-grade inflammation, entero-endocrine cell hyperplasia) [8]. However, the changes in microbiota in PI-IBS seem to differ from those described in IBS patients in general.

CORRELATION BETWEEN LEVEL OF CHANGE OF GUT MICROBIOTA AND IBS SYMPTOM SEVERITY (C)

Very few studies have tried to correlate IBS symptom severity with the degree of change in gut microbiota composition, also referred to as "dysbiosis". Most of them failed to identify significant correlations between differences in fecal microbiota abundance or composition and IBS symptom severity [7, 9]. In a large IBS patient dataset, the Gothenburg group used machine learning to identify an intestinal microbial signature that is able to predict IBS symptom severity [9], hinting at a quantitative relationship between gut microbiota alterations and IBS severity. However, confirmation is needed from other studies, and perhaps these should include non-tertiary care patient samples, where the variation in symptom severity may be larger.

INDUCTION OF IBS SYMPTOMS IN HEALTHY SUBJECTS THROUGH CHANGES IN GUT MICROBIOTA (D)

The fourth plausibility criterion, as described in the initial manuscript [6], is one of the most difficult to fulfill. There are very few suitable data for the different candidate pathophysiological mechanisms, and this also applies to gut microbiota alterations as a mechanism. The most supportive observation is probably derived from development of IBS after treatment of a non-gastrointestinal infection with systemic antibiotics [10]. The nature of the disturbance of gut microbiota after antibiotics, and the degree of similarity with gut microbiota in IBS are still unknown.

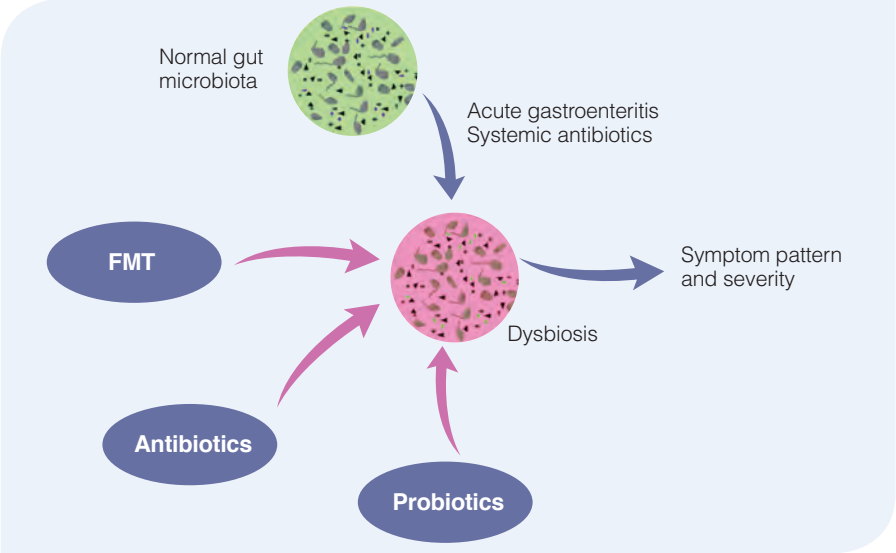
RESPONSE TO TREATMENT THAT TARGETS GUT MICROBIOTA COMPOSITION (E)

This section is the most extensively studied one when considering plausibility criteria for altered gut microbiota composition as a pathophysiological mechanism in IBS.

▼ FIGURE 2

Pathophysiological relevance of changes in gut microbiota in irritable bowel syndrome.

Normal gut microbiota composition reflects the state of health, without IBS symptoms. Acute events, such as an acute gastroenteritis or intake of systemic antibiotics may alter gut microbiota composition, leading to IBS symptoms. This may be therapeutically corrected by the use of non-absorbable antibiotics, probiotics or fecal microbiota transfer.



One line of evidence is the beneficial therapeutic effect of poorly absorbable antibiotics, clearly targeting gut microbiota [11, 12]. Two studies with neomycin and five trials with rifaximin showed efficacy of these poorly absorbable broad spectrum in non-constipated IBS patients [11-14]. In addition, a trial evaluating the safety and efficacy of repeat treatment with rifaximin confirmed as well the feasibility of this therapy upon symptom recurrence [15].

Probiotics are defined as preparations with living micro-organisms that confer a health benefit to the host when administered in adequate amounts. Several meta-analysis confirmed the efficacy of probiotics, as a group, to improve symptoms of IBS [11, 16]. However, the heterogeneity of study designs and endpoints, and the relative paucity of studies with specific probiotic types preclude making strong conclusion at the level of individual preparations. In contrast, prebiotics, substrates that are selectively utilized by host microorganisms conferring a health benefit to the host, showed no efficacy in improving IBS symptoms based on recent meta-analyses [11, 17].

Fecal microbiota transplantation (FMT) is probably the most direct way of targeting the gut microbiota for symptom control in IBS [18]. Studies to date have yielded highly variable outcomes, from no effect to symptomatic benefit, but also worsening of symptoms, generating conflicting conclusions in meta-analyses [19, 20]. However, recent studies have shown FMT-induced changes in gut microbiota composition associated with (transient) symptomatic benefit, and have implicated donor selection as a critical issue [21, 22].

UNSOLVED ISSUES AND FUTURE STUDIES

Taken together, changes in gut microbiota composition seem to fulfill the plausibility criteria for pathophysiological relevance in the irritable bowel syndrome [6]. The findings are summarized (**Figure 2**). However, there is a clear need for additional knowledge and research. More quantitative and better controlled studies characterizing the gut microbiota in IBS and controls are needed, and these should preferably include large patient cohorts also from primary care. This will allow a better understanding of the changes in gut microbiota in IBS at all levels of care, and has the potential to confirm a correlation between the magnitude of changes in gut microbiota composition and IBS symptom severity. In addition, longitudinal studies in

▼ TABLE 1

Highlight box: Summary of fulfillment of plausibility criteria for altered gut microbiota in IBS.

CRITERION	EVIDENCE	LEVEL OF EVIDENCE	REFERENCES
A **Presence**	A systematic review summarized the literature on significant differences in gut microbiota in patients with IBS compared with controls	Several papers reporting differences in gut microbiota composition in IBS versus health. Summarized in a recent meta-analysis (Level 5)	[7]
B **Temporal association**	The best evidence is found in the clinical entity of post-infection IBS	Several papers documenting increased occurrence of IBS after an acute (bacterial) gastro-enteritis. Summarized in the 2019 Rome Working team paper. (Level 5)	[8]
C **Correlation**	An intestinal microbial signature associated with IBS symptom severity has been described	Limited data so far: only one report claiming a correlation of microbiota profile with IBS severity. (Level 2)	[9]
D **Induction**	There is a paucity of data on this aspect. One supportive observation is the onset of IBS after systemic antibiotic intake	No data supporting this. Only the reported triggering by antibiotics in one paper (Level 1)	[10]
E **Therapeutic response**	This aspect is supported by beneficial therapeutic effects of poorly absorbable antibiotics, probiotics and fecal microbiota transplantation in IBS	Several studies in the literature reporting beneficial effects of microbiota-targeting therapeutic interventions in IBS. Some supported by meta-analysis. (Level 5)	[11-22]

IBS will be needed to further establish the temporal relationship between gut microbiota changes and symptom pattern and severity over time, in or outside the frame of a treatment trial.

There is a continued need for higher quality probiotic trials in IBS, using appropriate treatment lengths and validated endpoints, similar to those with pharmacological agents. Finally many new data on the use of FMT in IBS are expected, with a potential to clarify the best modalities and the efficacy of this treatment option.

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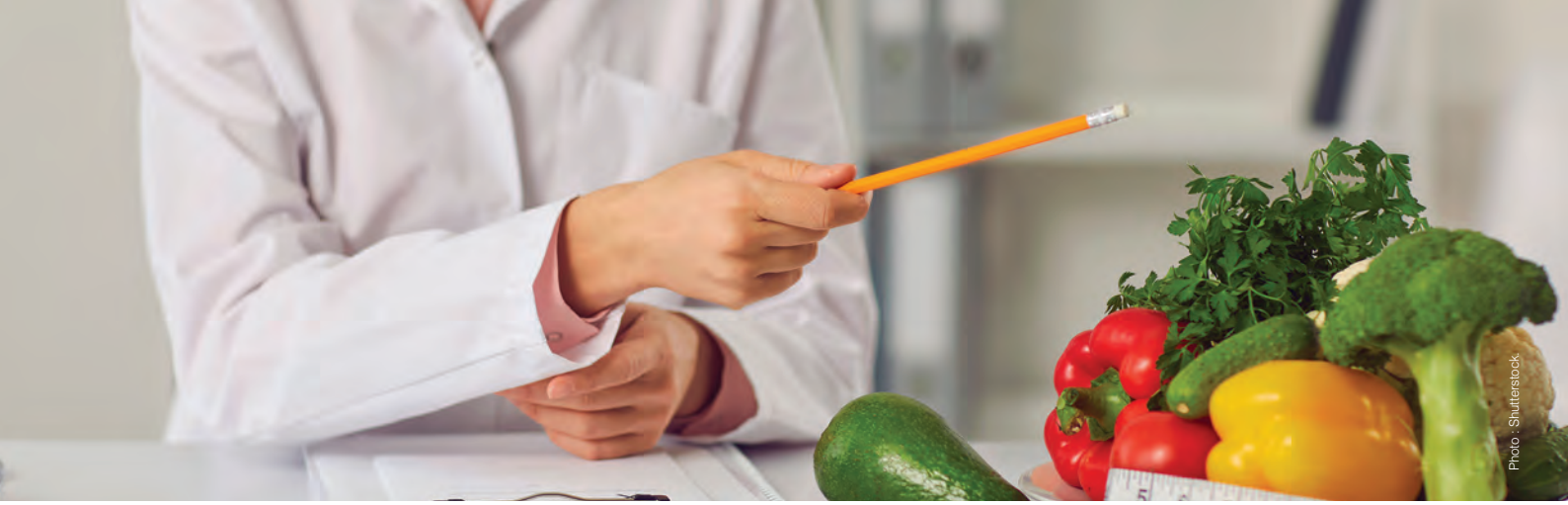

COMMENTED ARTICLE
ADULTS' SECTION

By Pr. Harry Sokol
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GUT-MICROBIOTA-TARGETED DIETS MODULATE HUMAN IMMUNE STATUS

Comments on the article by Wastyk et al. Cell 2021 [1]

Diet modulates the gut microbiome, which in turn can impact the immune system. In this article, the authors determined how two microbiota-targeted dietary interventions (one involving enrichment with plant-based fibre and the other fermented foods) influence the human microbiome and immune system in healthy adults. Using a 17-week randomised, prospective study (n = 18/arm) combined with omics-based measurements of microbiome and host, including extensive immune profiling, the authors identified diet-specific effects. High-fibre diet increased the number of microbiome-encoded degrading carbohydrate active enzymes (CAZymes) despite having no effect on microbial community diversity. Although cytokine response score was unchanged, "immunological" response in high-fibre consumers was observed and depended on baseline microbiota. However, the high-fermented-food diet steadily increased microbiota diversity and decreased inflammatory markers. The data highlighted how coupling dietary interventions to extensive and longitudinal immune and microbiome profiling can provide individualised and population-level information. Fermented foods may be valuable in countering decreased microbiome diversity and increased inflammation, which are pervasive in industrialised societies.

WHAT DO WE ALREADY KNOW ABOUT THIS SUBJECT?

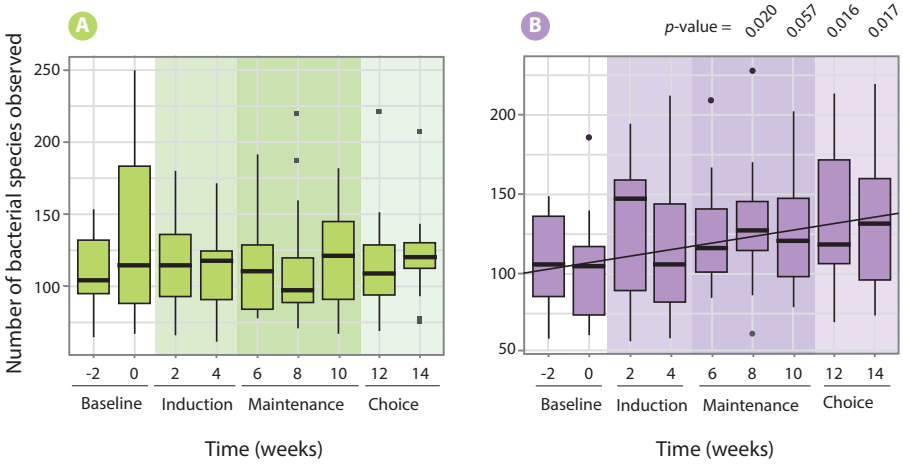
In humans, the link between diet and microbiota has been demonstrated in a number of ways, including by correlating dietary habits and the diversity or composition of the microbiota [2]. Short-term changes in diet can also rapidly change human gut microbiota [3]. Given that the microbiota plays a major role in human biology, its management, especially through nutritional interventions, could represent a major way of changing various aspects of health. A key question is to determine whether general (not personalised) dietary recommendations can be issued based on existing microbiota-host interactions to improve the health of populations. Many chronic non-communicable diseases, whose incidence is rapidly increasing with industrialisation, are linked to chronic inflammation. Industrialisation-related changes in gut microbiota are also well documented. Given the influence of the microbiota on inflammatory status, it is possible that a microbiota-targeted diet could reduce systemic inflammation. Many publications have confirmed the role of fibre in health, particularly by stimulating microbiota diversity along with the positive role of short-chain fatty acids, which are a product of their fermentation by the microbiota. Dietary fibre enrichment has an impact on the microbiota and improves health markers [4]. These results and the inadequate fibre intake in the average Western diet suggest that fibre intake may be a way to modulate the human immune system via the microbiota. Several reports suggest that fermented foods, such as kombucha, yoghurt and kimchi, may offer health benefits, including weight maintenance and reducing the risk of diabetes, cancer and cardiovascular diseases [5].

KEY POINTS

- The multi-omic study of the effects of a nutritional intervention reveals links between diet, microbiota and immunity
- High-fibre diet leads to functional changes in microbiota and immune response dependent on the baseline microbiota
- High-fermented-food diet increases microbiota diversity and decreases systemic inflammatory markers

▼ FIGURE 1

Number of bacterial species observed
A. Fibre consumption in the high fibre diet group.
B. Consumption of fermented foods in the high fermented food diet group.



WHAT ARE THE MAIN INSIGHTS FROM THIS STUDY?

To examine the effect of diet on the microbiome and immune system, healthy adults were recruited to participate in a 10-week dietary intervention programme (18 subjects per group). Participants were given either a high-fibre diet (an average increase from 21.5 ± 8.0 g daily to 45.1 ± 10.7 g daily) or a diet rich in fermented foods (an average increase from 0.4 ± 0.6 to 6.3 ± 2.9 portions daily). Surprisingly, a high-fibre diet did not increase microbiota diversity (**Figure 1A**), possibly due to an insufficient capacity of the microbiota of participants to breakdown carbohydrates. However, an increase in the abundance of plant carbohydrate-degrading enzymes was reported. Decreased branched-chain fatty acids (isobutyric, isovaleric and valeric acid) was observed, although it was impossible to determine whether this finding was due to a functional change in the microbiota or a decrease in the consumption of dairy products and beef, which contain high levels of these molecules. A diet-related effect on the immune profile was observed and was dependent on the baseline microbiota of the participants.

Unlike a high-fibre diet, a diet rich in fermented foods increased microbiota diversity (**Figure 1B**). This increase was not primarily related to the colonisation of the probiotic bacteria consumed, but rather to the acquisition of new bacteria or the expansion of certain endogenous bacteria. Finally, the consumption of fermented food resulted in decreased systemic inflammatory levels with a decrease in several cytokines, chemokines and other inflammatory serum proteins, including interleukin IL-6, IL-10 and IL-12b.

CONSEQUENCES IN PRACTICE?

This study showed that diet has profound effects on gut microbiota and host physiology, thus confirming its role in health and potential disease-prevention. The effects of diets rich in fibre and fermented foods differ widely. Improving the definition of the effects of diet on the microbiota and host physiology will allow preventative or therapeutic strategies to be implemented on both a population-wide and individual level.

CONCLUSION

This prospective randomised study evaluating the effect of a diet enriched with fibre or fermented foods shows the specific effects of each type of diet on the microbiota and host immunity, thus confirming the key role of diet in health, particularly through its effects on gut microbiota.

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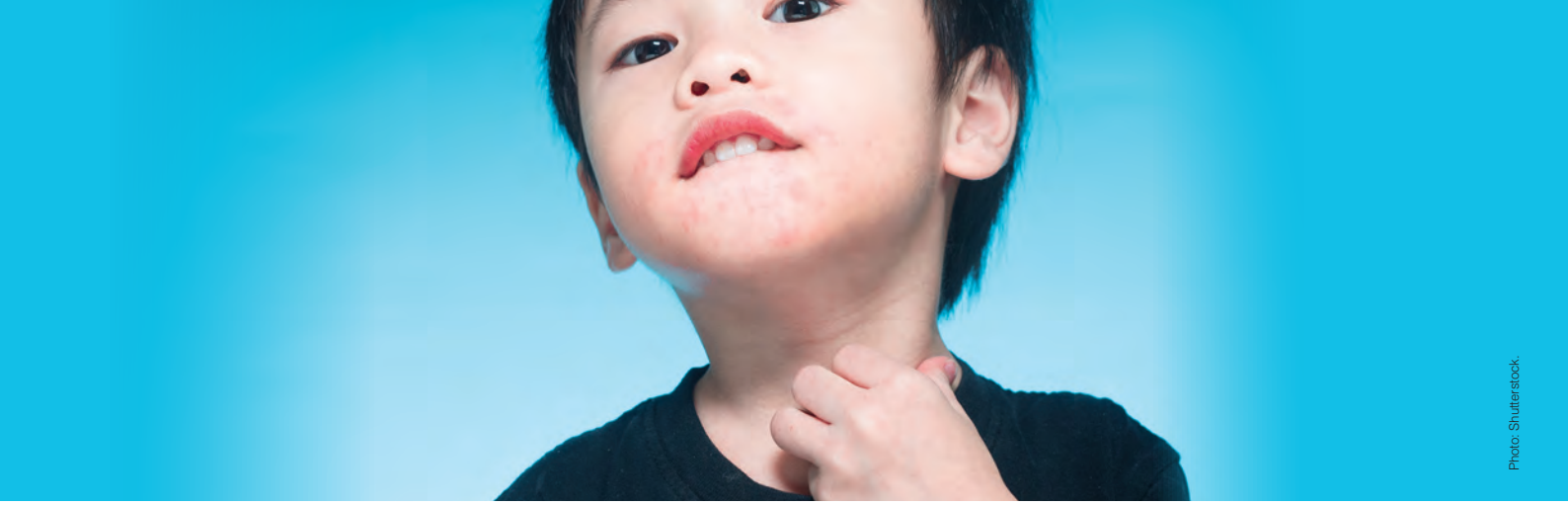

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COMMENTED ARTICLE
CHILDREN'S SECTION

By Pr. Emmanuel Mas
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ETHNICITY ASSOCIATIONS WITH FOOD SENSITISATION ARE MEDIATED BY GUT MICROBIOTA DEVELOPMENT IN THE FIRST YEAR OF LIFE

Comments on the original article by Tun HM et al. Gastroenterology 2021 [1]

Increasing evidence supports the role of early-life gut microbiota in the development of atopic diseases, but ecological changes to gut microbiota during infancy related to food sensitisation remain unclear. The authors sought to characterise and associate these changes with the development of food sensitisation in children. In this observational study, the authors used 16S rRNA sequencing to characterise the composition of 2,844 faecal microbiota in 1,422 Canadian full-term infants. Atopic sensitisation outcomes were measured by skin prick tests at the ages of 1 year and 3 years. Four developmental trajectories of gut microbiota were identified shaped by birth mode and by ethnicity.
This study established a link between persistence of low *Bacteroides* abundance in the gut throughout infancy and peanut sensitisation in childhood. It is the first study to show a mediation role for infant gut microbiota in ethnicity-associated development of food sensitisation.

WHAT DO WE ALREADY KNOW ABOUT THIS SUBJECT?

The number of children with food allergies is increasing rapidly, currently representing 28% of children aged 1-5 years in the United States. The development of the gut microbiota (GM) in the first months of life may be involved in this sensitisation to food allergens [2]. Many factors influence the establishment of GM, such as the mode of delivery (caesarean versus vaginal), type of breastfeeding (breast or formula) and use of antibiotics [3, 4]. A recent study showed that GM structure also varied widely between different ethnic groups [5].

Transferring GM from healthy children to mice was shown to protect them from cow's milk allergy. Low GM richness in young infants and a high ratio of *Enterobacteriaceae/Bacteroidaceae* (E/B) in early and late infancy are predictors of food allergen sensitisation [6].

WHAT ARE THE MAIN INSIGHTS FROM THIS STUDY?

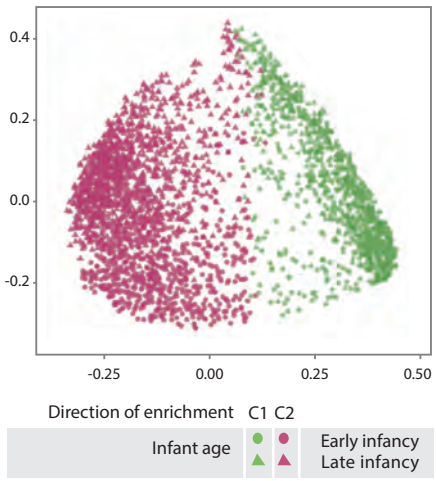
The study included 1,422 children from the CHILD (*Canadian Healthy Infant Longitudinal Development*) cohort. Prick tests were performed (inhalant and food allergens) at the ages of 1 and 3 years. Stool samples were collected in early (3.5 ± 0.9 months) and late (12.2 ± 0.3 months) infancy.

Atopy prevalence was 12% at 1 year and 12.8% at 3 years, with 9.5% and 5.8% of food sensitisation and 3.3% and 10.1% of sensitisation to inhalant allergens at ages 1 and 3 years, respectively.

Late infancy GM had lower beta-diversity and intra-individual variability compared to early infancy GM ($p < 0.001$). Late infancy gut microbiota were enriched with *Bacteroides, Faecalibacterium, Lachnospira, Prevotella*, unclassified *Lachnospiraceae* and unclassified *Clostridiales*, but depleted with *Clostridium, Veillonella, Bifidobacterium* and unclassified *Enterobacteriaceae*. The principal component analysis identified two clusters (C1 and C2, **Figure 1**). C1 was composed of 75.5% of early infancy samples and C2 of 63.7% of late infancy samples. These early and late infancy samples representing vaginal births without intrapartum antibiotic prophylaxis were of type C2, dominated by the genus *Bacteroides* (**Figure 2**).

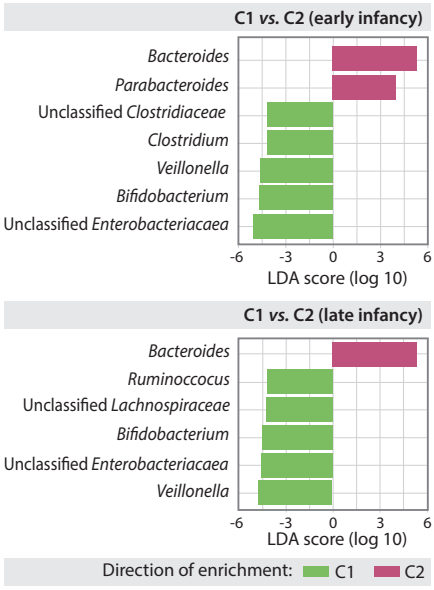
▼ FIGURE 1

C1 and C2 gut microbiota clusters (principal component analysis).



▼ FIGURE 2

Composition of gut microbiota in early and late C1 and C2 clusters in infants.



The authors identified four trajectories according to the type of early and late infancy cluster: C1-C1, C1-C2, C2-C1 and C2-C2. The C1-C1 trajectory was more common among Asian than Caucasian infants ($p < 0.05$), as well as in atopic-risk children compared to the C2-C2 (OR 1.9; 95% CI 1.15-3.14) or C1-C2 (OR 2.38; 95% CI 1.43-3.96) trajectory. Infants in the C1-C1 trajectory were twice as likely to have food sensitisation at the age of 3 years compared to those in the C2-C2 trajectory (OR 2.34; 95% CI 1.20-4.56) and C1-C2 trajectory (OR 2.60; 95% CI 1.33-5.09), especially to peanuts (vs C2-C2 = OR 2.82; 95% CI 1.13-6.01 and vs C1-C2 = OR 2.01; 95% CI 0.85-4.78) (**Figure 3**). Children who had not acquired peanut sensitisation at the age of 3 years had persistently higher levels of *Bacteroides* ($p = 0.044$), lower levels of unclassified *Enterobacteriaceae* ($p = 0.001$) and a lower E/B ratio ($p = 0.013$) throughout childhood.

The C1-C1 trajectory mediated the risk of food and peanut sensitisation in Asian children. The association was even high for peanuts (OR 7.87; 95% CI 2.75-22.55). Infants in the C1-C1 trajectory were more often colonised with *C. difficile*. These same children, with both the C1-C1 characteristic and colonised with *C. difficile,* had an extra risk of food (OR 5.69; 95% CI 1.62-19.99) and peanut (OR 5.89; 95% CI 1.16-29.87) sensitisation.

Finally, microbiota of the C1-C1 trajectory had a deficiency in sphingolipid metabolism and glycosphingolipid biosynthesis-related functions.

WHAT ARE THE CONSEQUENCES IN PRACTICE?

This study allows us to envisage GM-targeted therapies for food allergies in infants, either as a preventative or therapeutic option.

KEY POINTS

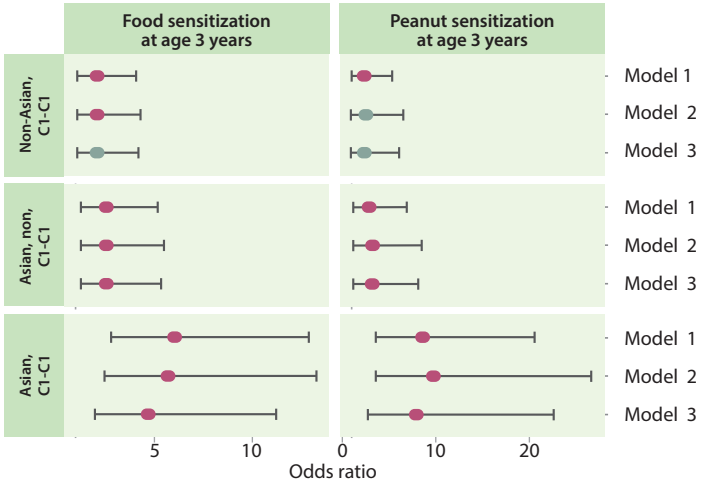
- During the development of the gut microbiota in the first year of life, persistently low levels of *Bacteroides* increase the risk of food sensitisation, especially to peanuts
- This risk is increased in neonates of Asian mothers

CONCLUSION

This study showed different developmental trajectories of the gut microbiota in the first year of life. It confirms the impact of the birth mode on gut microbiota. Persistently low levels of *Bacteroides* were associated with a risk of food sensitisation, particularly in neonates of Asian mothers or those colonised with *C. difficile*.

▶ FIGURE 3

Food and peanut sensitisation at the age of 3 years according to the C1-C1 trajectory and Asian origin of the mother



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By Dr. Genelle Healey
BC Children's Hospital Research Institute
University of British Columbia
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COULD THE GUT MICROBIOME BE TARGETED TO OPTIMIZE SARS-COV-2 VACCINE EFFICACY?

The primary goal of a successful SARS-CoV-2 vaccine, which is the main hope in controlling the Covid-19 pandemic, is to confer robust and long-lasting immunity for as many people administered the vaccine as possible. Despite several vaccines being deployed worldwide to manage the SARS-CoV-2 pandemic ongoing Covid-19 outbreaks demonstrate that the pandemic is far from over. Development of novel strategies to help control the spread of the virus and/or enhance the efficacy of SARS-CoV-2 vaccines may prove useful in the fight against Covid-19.

SARS-COV-2 VACCINE EFFICACY

Vaccines are administered to challenge both the innate and adaptive immune systems. One common biomarker of lasting immunity and protection against SARS-CoV-2 are antibody responses. For reasons still poorly understood antibody responses to SARS-CoV-2 vaccination are highly variable between different people [1]. Based on results from clinical trials SARS-CoV-2 vaccine efficacy for approved vaccines ranges from around 60 to 92% against the original SARS-CoV-2 strains but vaccine-induced protection towards SARS-CoV-2 variants of concern (*i.e.*, alpha, beta, delta, and gamma) appears to be lower [2]. Heterogenicity in vaccine responses between people, reduced vaccine efficacy with variants of concern and potential waning of vaccine efficacy over time all compromise the continued efforts to control the spread of SARS-CoV-2. Therefore, gaining a better understanding of the factors driving variations in SARS-CoV-2 vaccine efficacy in the short and long term is fundamentally important.

FACTORS THAT AFFECT VACCINE IMMUNOGENICITY

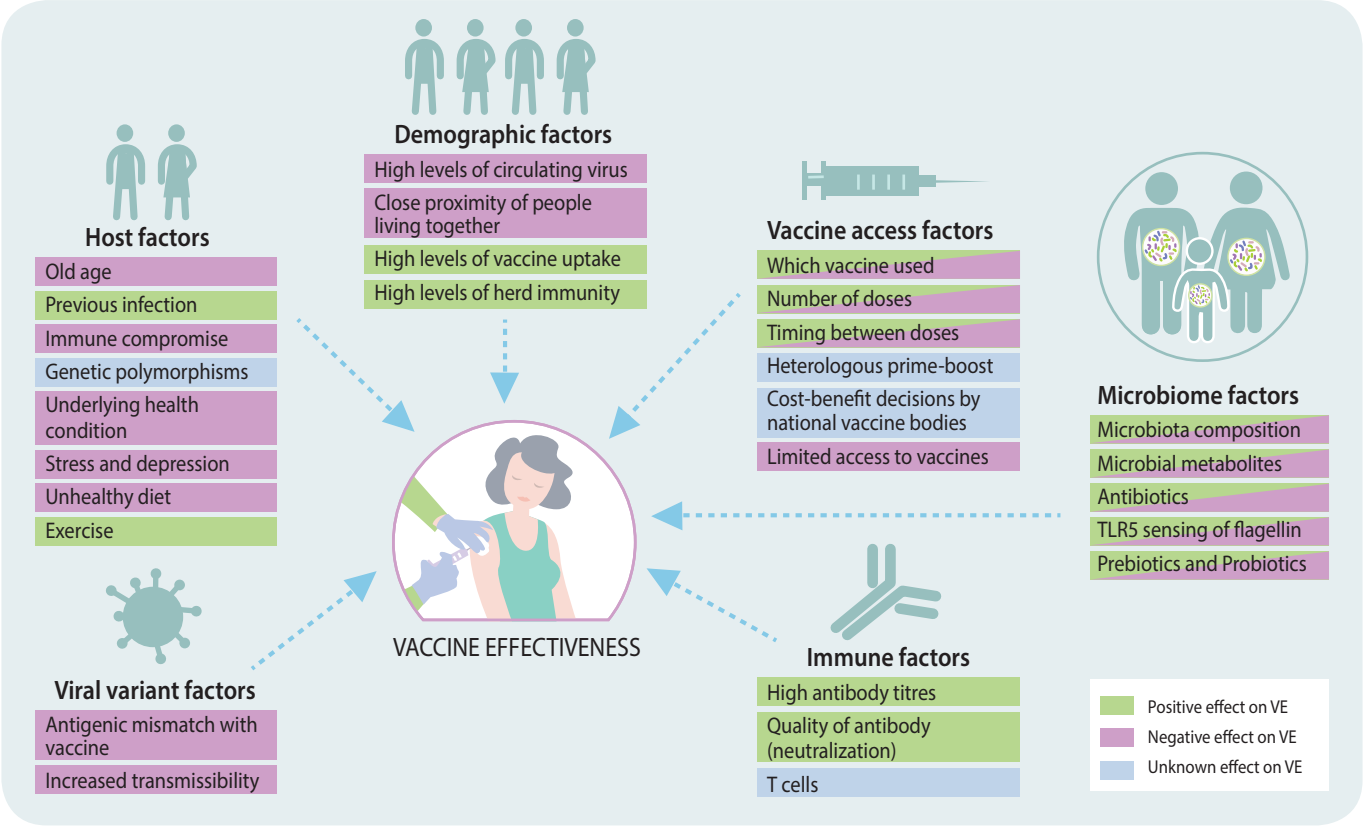
Given that everyone receives the same standardised vaccine dose, but immune responses vary widely, it is highly likely that factors other than vaccine type effect vaccine efficacy. Mounting evidence suggests that factors such as age, chronic disease, poor health behaviours, depression, and stress impact the immune system's ability to respond to vaccines (**Figure 1**) [3-5]. These findings have been demonstrated across several vaccine types, so it is likely translatable to SARS-CoV-2 vaccines. Interestingly, most of the factors outlined above have also been shown to impact the composition and functional capacity of the gut microbiome. It is, therefore, plausible that gut microbiome dysbiosis driven by host factors could be implicated in the differing vaccine responses observed.

TARGETING THE GUT MICROBIOME TO ENHANCE VACCINE EFFICACY?

The gut microbiota is a collection of bacteria, fungi, viruses, and archaea that reside in the gastrointestinal tract and have co-evolved with their host over time. These microbes perform many important functions, one of which is regulating local and systemic immune responses. Interestingly, certain gut microbiota profiles (*i.e.*, higher abundance of Actinobacteria, *Clostridium* cluster XI and Proteobacteria) have been associated with greater vaccine immunogenicity against viral infections such as HIV, influenza, and rotavirus [6-8]. A recent study reported that antibiotic-specific disruption of the gut microbiome (*i.e.*, dysbiosis) led to impaired post influenza vaccine-induced antibody neutralization as well as lower concentrations of vaccine-induced antibody responses [9]. Another study using both antibiotic treatment and germ-free mice demonstrated that sensing

▼ **FIGURE 1**

Factors influencing vaccine effectiveness.
Adapted from [14].



of a bacterial motility component (flagellin) by a receptor found on immune cells (toll-like receptor 5 [TLR5]) was necessary in promoting a robust vaccine response [8]. This and other similar studies [10] provide evidence of the important role the gut microbiota plays in vaccine efficacy (**Figure 1**). However, to date no studies have investigated what impact the gut microbiota has on SARS-CoV-2 vaccine efficacy. Thus, future research which determines whether specific gut microbiota signatures impact SARS-CoV-2 vaccine efficacy are paramount. Additionally, microbiome-targeted therapies, *i.e.*, prebiotics and probiotics [11], could be utilized as a vaccine adjuvant (an agent used to accelerate, enhance and/or prolong antibody specific immune responses) to enhance SARS-CoV-2 vaccine immunogenicity. Specifically, intranasal administration of lactic-acid bacteria (*e.g., Bifidobacterium and Lactobacillus*) has been shown to enhance resistance to viral infections and improve influenza vaccine efficacy [12, 13], therefore, oral delivery of live bacteria (probiotics) could boost vaccine specific immune responses if given alongside SARS-CoV-2 vaccines.

CONCLUSION

Irrespective of global vaccine deployment and targeted public health measures the Covid-19 pandemic continues to persist. Vaccines are the main hope in controlling SARS-CoV-2; however, heterogeneity in vaccine responses compromises the fight against Covid-19. Several gut microbiome factors have been implicated in altering vaccine immunogenicity. Therefore, utilisation of the gut microbiome as a vaccine adjuvant has the potential to improve SARS-CoV-2 vaccine effectiveness.

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VIRTUAL APDW 2021

ASIAN PACIFIC DIGESTIVE WEEK

Vision of Excellence in Digestive Disorders & Sciences

CONGRESS REVIEW

By Pr. Fergus Shanahan

Department of Medicine, University College Cork, National University of Ireland, Cork, Ireland; APC Microbiome Ireland, University College Cork, National University of Ireland, Cork, Ireland

AUGUST 2021

HIGHLIGHTS FROM THE APDW 2021

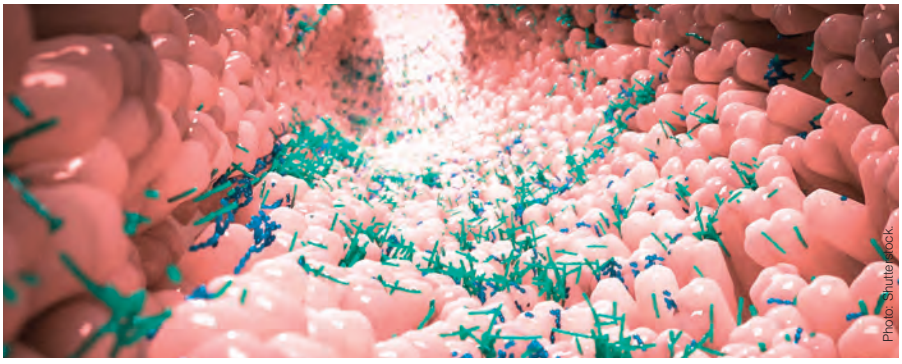
During the Asian Pacific Disease Week (APDW), while Covid-19 restrictions limited human contact everywhere on the planet, a special virtual satellite symposium addressed the changing nature of modern society on the microbiome, including the impact of social distancing and the consequences for health and risk of disease.

Pr. Fergus Shanahan (*University College Cork, APC Microbiome Ireland*) introduced the concept of the "social microbiome" which includes the factors promoting transmission and sharing of microbes within human social networks [1]. He emphasised that the consequences of social influences on the microbiome are likely to be most evident in the elderly. Aloneness, life indoors, institutional care and loss of human contact – all of which were increased during Covid-19 – are among the factors leading to a deterioration in the health of the microbiome with age. Emphasising the need for more research on the lifestyle and environmental influences on the microbiome, he observed that most of the variance in the human microbiome remains unaccounted for.

Pr. Martin Blaser (*Rutgers University, NJ, USA*) then outlined the known influences on the composition of the human microbiome, and illustrated his ground-breaking research on the adverse effects of antibiotics. Progressive loss of ancestral microbes has occurred since the introduction of antibiotics [2]. This has been associated with the increased frequency of non-communicable chronic diseases, including immune and metabolic disorders. While the causal nature of these associations is unproven, Pr. Blaser reviewed his own experimental work which provides clear evidence for permanent, long-term and even trans-generational adverse effects of antibiotics on the microbiome and host health.

Pr. Francisco Guarner (*Vall d'Hebron Research Institute, Barcelona, Spain*) showed how gut microbes shape mucosal and systemic immune responses and particularly how a healthy gut microbiome promotes tolerogenic rather than immunogenic host responses. He pointed out that the clinical significance of this is shown by the impact of the microbiota on responses to immunotherapy in patients with cancer and how antibiotics may alter immunity to vaccines [3]. Pr. Guarner also showed the influence of certain probiotics on host immune responses.

In discussion, the speakers highlighted the clinical importance of retaining biodiversity within the gut. In addition to limiting injudicious use of broad-spectrum antibiotics, the role of dietary diversity as a simple personal measure for maintaining gut microbial diversity, was emphasised. There was a consensus that therapeutic modulation of the microbiota is a realistic prospect. While the promises of microbiome science are extensive, many gaps in knowledge persist [4]. Unknowns such as the long-term consequences of social distancing represent opportunities to explore the importance of the microbiome on health and disease in all sectors of society.



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CONGRESS REVIEW

OCTOBER 2021

HIGHLIGHTS FROM THE UEG WEEK 2021

By Pr. Erick Manuel Toro Monjaraz
Instituto Nacional de Pediatría, INP Department of Gastroenterology, Mexico City, Mexico

The UEG week is the European Gastrointestinal Congress where the last advances in Gastroenterology all over the world, especially in microbiota are shown; the high quality of the works presented made it difficult to choose those covered in this paper.

TARGETING THE GUT MICROBIOTA IN IBS

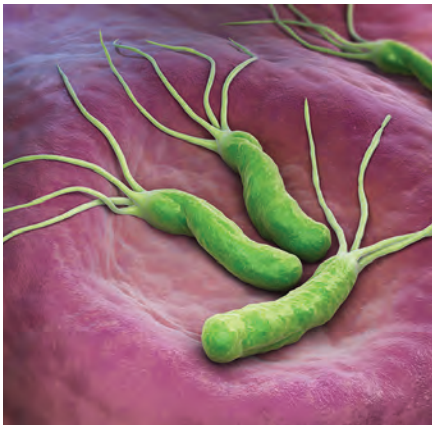
Dr. Gerard Clark, focusing on the interaction and role of microbiota in the IBS, showed in his presentation that the microbiota regulates visceral pain in the mouse. Germ-free animals have an exaggerated stress response, and probiotics reduce the stress-induced cortisone levels. Many mechanisms explain this interaction; one of them is serotonin. Dr. Clark presented a paper by Marco Constante that demonstrated that microbiota from IBS subjects with comorbid anxiety induced both GI dysfunction and anxiety-like behavior in recipient animals. This scenario opens the opportunity to use prebiotics, probiotics, and fermented foods as psychobiotics (probiotics with effect in central nervous system), helping in IBS symptoms and the psychiatric conditions associated with IBS [1].

RESISTOME IN *HELICOBACTER PYLORI* ERADICATION

As we know, antimicrobial resistance is a cause of concern, and gut microbiota is a reservoir of antimicrobial resistance genes. In previous studies, diet and foods that offer health benefits beyond their nutritional value known as functional food, modify the gut resistome with promising results. Specific probiotic strains have shown to decrease the abundance of multi resistant bacteria. In Quito, Ecuador, Dr. Cifuentes, and her group compared the fecal resistome of patients treated for *H. pylori* eradication (triple therapy) with and without specific probiotic strain added to treatment. They demonstrated that adding specific probiotic strain reduces the presence of antimicrobial resistance genes; the mechanism proposed is the modulation of the gut microbiota and the immune system and the production of fatty acids with antimicrobial and inhibitory properties of conjugation [2].

CAN WE PREVENT INFLAMMATORY BOWEL DISEASE BY TARGETING GUT MICROBIOTA?

Pr. Marla Dubinsky presented a lecture that tries to answer this question. There is an increasing incidence of inflammatory bowel disease (IBD) in very young children and increasing incidence in 2nd



generation of immigrants coming from low to high incidence IBD areas, probably associated with changes in the gut microbiota; there is evidence of the role of the gut microbiota in the genesis of IBD, for example in the MECONIUM study perform by Torres J *et al.*, they show that babies of mothers with IBD have a different microbiota compared with healthy children; Also, the diet has a specific role in IBD, specifically, by modulating microbiota; the western diet is proinflammatory with lower *Prevotella* spp; this change leads to an endotoxins increase. In conclusion, with technology advances, in the future, we can identify specific microbiota populations and prevent IBD without adverse events [3].

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PRESS REVIEW

By Pr. Markku Voutilainen
Turku University Faculty of Medicine; Turku University Hospital, Department of Gastroenterology, Turku, Finland

GUT MICROBIOTA

FECAL MICROBIOTA TRANSPLANTATION AND FIBER SUPPLEMENTATION TO CONTROL METABOLIC SYNDROME IN OBESE PERSONS

Obesity and metabolic syndrome (MS) comprise one of the greatest health epidemics of the 21st century. MS is associated with increased risk of cardiovascular diseases and all-cause mortality. To establish FMT as a pragmatic therapy for obesity and metabolic syndrome, novel strategies using non-invasive delivery methods in patients suffering metabolic dysfunction are needed. The authors tested oral FMT and dietary fibres supplementation to improve insulin sensitivity. In this double-blind randomized phase II trial, 70 severely obese patients with MS were randomized in four groups. The 1st and 2nd groups received single-dose oral encapsulated FMT followed by high-fermentable (HF) or low-fermentable fiber (LF) supplement for 6 weeks, respectively. The 3rd and 4th group received placebo and HF or LF supplementation. The primary outcome was the evaluation of changes in insulin sensitivity between baseline and after 6 weeks of treatment using the homeostatic model assessment (HOMA2-IR/IS).

No serious adverse effects were reported during the intervention. After 6 weeks, insulin sensitivity improved only in the FMT-LF group insulin levels also improved, but fasting glycemia, glycated haemoglobin and anthropometric values did not change. FMT resulted increased gut microbial richness, the change was greatest in the FMT-LF group. *Phascolarcobacterium, Bacteroides stercoris* and *B. caccae* were associated with HOMA2-IR and insulin sensitivity and may be used for future treatment.

Photo: AdobeStock

Mocanu V, Zhang Z, Deehan EC, *et al.* Fecal microbial transplantation patients with severe obesity and metabolic syndrome: a randomized double-blind, placebo-controlled phase 2 trial. *Nat Med* 2021; 27: 1272 -9

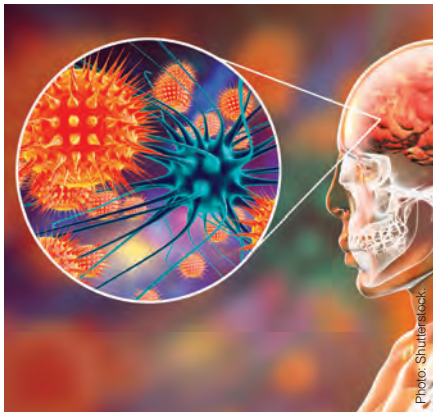
GUT MICROBIOTA, EPITHELIAL DEFENCE AND NEONATAL BACTERIAL MENINGITIS

Group B streptococcus (GBS) is a leading cause of meningitis, pneumonia and sepsis in infants, and 68% of GBS neonatal meningitis are late-onset infections (developing from 7 days to 3 months after birth). This infection may result from intestinal GBS colonization transmitted from mother to child during pre- or post-delivery.

The authors examined in mice the reasons of neonatal susceptibility to GBS and showed that it was associated with gut microbiota dependent/independent factors as well as age. Mature gut microbiota resists GBS colonization, strengthens gut barrier function limiting GBS invasion and plays a central role in the maturation of immune system. In neonatal gut, age-dependent Wnt pathway activity in intestinal and choroid plexus epithelia favors GBS translocation due to lower cell-cell junctions polarization. Moreover, gut microbiota

immaturity is associated with decreased resistance to GBS colonization and increased vascular-gut barrier permeability, which favors bacteremia.
The authors suggest that maturing neonatal microbiota with probiotics and/or prebiotics may help in preventing neonatal bacterial meningitis.
In conclusion, fluoroquinolone prophylaxis gives short-term protection against infections but does not increase the risk of cross-resistance to other antibiotics.

Travier L, Alonso M, Andronico A, *et al.* Neonatal susceptibility to meningitis results from the immaturity of epithelial barriers and gut microbiota. *Cell Rep* 2021; 35(13): 109319.



MICROBIOTA, STRESS AND SOCIAL BEHAVIOUR

The microbiota-gut-brain axis (MGBA) is a two-way communication system linking the gut microbiota and brain. MGBA modulates behavior such as sociability and anxiety in mice, however underlying mechanisms remains unknown. In this article, antibiotic-treated mice and germ-free mice showed decreased social activity associated with increased corticosterone level. This stress hormone is produced by the activation of the hypothalamus–pituitary–adrenal axis (HPA). Gut bacteria transplantation from SPF (*Specific Pathogen-Free*) mice donors corrected social activity and lowered corticosterone level. Glucocorticoid receptors in the hypothalamus were negative regulators of the HPA axis These receptors regulated corticosterone levels and social behaviors, both of these functions were regulated by gut microbiota. In antibiotic-treated mice, genetic ablation of glucocorticoid receptors or chemogenetic inactivation of neurons producing the corticotrophin-releasing hormone (CRH) induce social behaviour reversal. Activation of CRH and glucocorticoid receptor-expressing neurons induced social behavior alterations in mice having normal microbiota, indicating neural pathway regulating social behavior. Finally, neomycin-sensitive bacteria, *e. g. Enterococcus faecalis*, mediates social behavior.
The present results suggest that specific bacteria prevent overactive stress reaction by attenuating corticosterone production mediated by HPA-axis. The detection of neural pathway mediating signals from the gut to the brain may enable procedures that modulate social behavioral disorders.

Wu WL, Adame MD, Liou CW, *et al.* Microbiota regulate social behavior via stress response neurons in the brain. *Nature* 2021; 595(7867): 409-14.

GUT MICROBIOTA AND BRAIN INFARCT

Clinical studies reported that circulating gut-microbiota derived metabolite trimethylamine-N-oxide (TMAO) are associated with stroke. However, the direct involvement of gut microbiota in cerebral vascular diseases (including stroke) is not known with certainty. Circulating TMAO is generated by microbial metabolism of TMA-containing precursors, including choline, which is commonly enriched in a Western diet. By using rodent models of stroke, the authors investigated whether gut microbiota in general or either TMAO or a functioning gut microbial *cut*C gene (choline utilisation [cut] c gene catalyzes choline-TMA transformation) can impact stroke severity. Germ-free mice were colonized with human gut microbiota from subjects with high or low serum TMAO levels followed by experimental stroke injury. The authors showed that stroke severity was transmissible, and TMAO levels correlated with stroke severity. Specific gut bacterial taxa positively correlate with high TMAO levels, brain infarct size through dietary choline. Gut microbial *cut*C gene increases host TMAO levels, cerebral infarct size, and functional deficits.
In summary, gut microbiota with choline-TMAO pathway increases stroke severity and worsens functional outcome. Western diet (and diet rich in red meat) contains TMA precursors and have been associated with stroke risk. Dietary interventions in patients with high stroke risk merit further investigation. *Cut*C activity is the key factor for stroke severity and TMAO pathway could be a potential target for the prevention or treatment of stroke.

Zhu W, Romano KA, Li L, *et al.* Gut microbes impact stroke severity via trimethylamine N-oxide pathway. *Cell Host Microbe* 2021; 29(7): 1199-1208.e5.

VAGINAL MICROBIOTA

IS THE VAGINAL MICROBIOTA TO BLAME FOR DYSMENORRHEA?

In a pilot study - the first to focus on the link between the composition of the vaginal microbiota during menstruation and the intensity of period pain - 20 women were classified into three groups according to the pain they experienced during their period: “mild localized pain”, “severe localized pain”, or “severe multiple pain and gastrointestinal symptoms”. The vaginal microbiota was analyzed both during menstruation and outside of menstruation. The results showed that the vaginal microbiota composition significantly varied between women as well as over the course of the menstrual cycle, but the composition during menstruation varied even more depending on intensity of pain. In particular, during menstruation, women with more severe dysmenorrhea had a lower abundance of lactobacilli and a higher abundance of potentially pro-inflammatory bacteria.


Photo: iStock

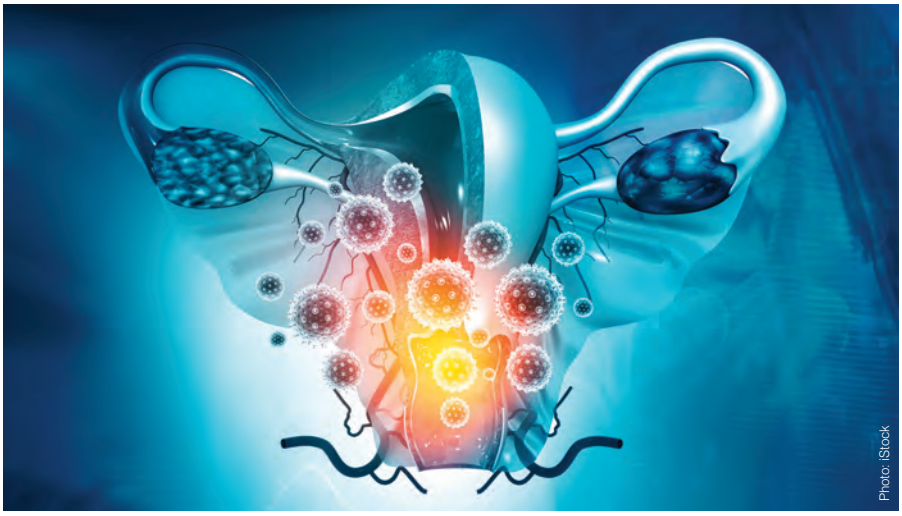
Although limited in terms of size, age groups studied and ethnic diversity, this pilot study is a first step towards larger studies on associations between the intensity of pain during menstruation and the composition of the vaginal microbiota. The researchers hypothesize that during menstruation endometrial tissue is broken down, releasing compounds (prostaglandins) that may cause uterine muscle contractions and increased sensitivity, thus contributing to menstrual pain. Certain bacteria in the vaginal microbiota may promote the release of these compounds and of pro-inflammatory cytokines that exacerbate the symptoms of dysmenorrhea. If these hypotheses are confirmed, the pilot study would underline the importance of taking into account inter-individual differences and the dynamics of the vaginal microbiota during the menstrual cycle.

Chen CX, Carpenter JS, Gao X, *et al.* Associations Between Dysmenorrhea Symptom-Based Phenotypes and Vaginal Microbiome: A Pilot Study. *Nurs Res* 2021 [Epub ahead of print].

CERVICOVAGINAL MICROBIOTA: A MARKER FOR PERSISTENT PAPILLOMAVIRUS INFECTION?

In this new study, the cervicovaginal microbiota of 15 women was analyzed via 16S rRNA gene sequencing, and HPV genotyping was performed. Six of the women showed persistent infection (infection with the same HPV type for more than 12 months), four showed transient infection (infection cleared in less than 12 months) and five were HPV-negative. The three groups showed significant differences in the composition of the cervicovaginal microbiota. In the healthy women and those with transient infection, the *Lactobacillus* genus predominated, whereas women with persistent infection had a more diverse cervicovaginal microbiota. A statistical analysis revealed 36 bacteria to be associated with transient or persistent infection status, with these bacteria having the potential to serve as biomarkers. Among them, and in line with previous studies, the genera *Acinetobacter, Prevotella* and *Pseudomonas* were correlated with persistent infection. On the other hand, *Lactobacillus iners* was correlated with transient infection. The women with persistent HPV infection had significantly higher concentrations of IL-6 and TNF-α in their cervical secretions and a higher number of regulatory T cells and myeloid-derived suppressor cells in their peripheral blood. The results of this study suggest that changes in the cervicovaginal microbiota may be linked to persistent HPV infection. However, it is not known whether dysbiosis induces persistence of the infection or vice versa. Despite this, the identification of a microbial signature for persistent HPV infection may allow earlier diagnosis, ultimately leading to earlier intervention to eradicate the infection and reduce the likelihood of developing malignant cervical lesions.

Qingqing B, Jie Z, Songben Q, *et al.* Cervicovaginal microbiota dysbiosis correlates with HPV persistent infection. *Microb Pathog* 2020; 152: 104617.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Want to stay informed about microbiota? Looking for a useful and trustful partner when it comes to information about research and clinical practice? Biocodex Microbiota Institute launches **www.biocodexmicrobiotainstitute.com/pro**. Available in 7 languages (English, French, Spanish, Russian, Polish, Turkish and Portuguese), this online international hub provides, in a dedicated section, Healthcare Professional with the latest scientific news and data about microbiota including the Institute's exclusive content such as Microbiota magazine, thematic folders, continuing medical education (CME) courses and interviews with experts. Want to go deeper with your patient? Promote the importance of microbiota on his/her health? Invite him or her to an online journey on the lay public section where they can find updated, useful and understandable contents. Convinced? So, take a tour on **www.biocodexmicrobiotainstitute.com/pro**.

THE BIOCODEX MICROBIOTA INSTITUTE JOINS THE WAAW CAMPAIGN 2021

It could ultimately undermine a century of medical progress[1]. The ticking health time bomb of antimicrobial resistance is in sights of the WHO, which has organized the annual World Antimicrobial Awareness Week (18–24 November) since 2015. As a major center of expertise on the microbiota, the Biocodex Microbiota Institute has been an active partner for the event since 2020. Throughout November, the Institute has shared exclusive articles and news, as well as expert videos and downloads on key topics, to enhance your knowledge and help you understand the mid- and long-term effects of antibiotics on the human microbiota.

[1] No Time to Wait: Securing the future from drug-resistant infections. Report to the secretary-general of the united nations. Avril 2019. **https://www.who.int/docs/default-source/documents/no-time-to-wait-securing-the-future-from-drug-resistant-infections-en.pdfsfvrsn=5b424d7_6**

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