



GUT MICROBIOTA
RESEARCH & PRACTICE
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SYNBIOTICS

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EDITORIAL



Dr. Mary Ellen Sanders

Mary Ellen Sanders is a consultant in the area of probiotic microbiology, with special expertise in paths to scientific substantiation of probiotic product label claims. Dr. Sanders served as the founding President of the International Scientific Association for Probiotics and Prebiotics (www.isappscience.org) and is currently the organization's Executive Science Officer.



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Probiotics—defined as “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host” (Hill *et al.*, 2014)—are among the first strategies used for modulating the gut microbiota. Initially consumed in the form of lactic ferments, live microbes had a century-old history before an expert panel officially coined the term in 2001 (FAO & WHO, 2001).

The concept of prebiotic is more recent and was introduced in 1995 by Gibson and Roberfroid (Gibson & Roberfroid 1995). In 2017, an updated definition of prebiotic was released: a substrate that is selectively utilized by host microorganisms conferring a health benefit. The main changes are that this new definition includes populations of bacteria other than *Lactobacillus* and *Bifidobacterium*; other targeting sites beyond the gut; and the inclusion of substances that are reported to have fermentation-independent health effects (e.g. human milk oligosaccharides and polyphenols) (Gibson GR *et al.*, 2017).

Synbiotics, meanwhile, are appropriate combinations of prebiotics and probiotics that are considered gut microbiota-management tools for improving host health (World Health Organisation, 2017). Gibson & Roberfroid were the first to anticipate that prebiotics and probiotics could be combined as synbiotics (Gibson & Roberfroid 1995). Afterwards, Kolida & Gibson



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proposed two ways in which synbiotics might act to enhance the effects of their component parts. The first consisted of a complementary approach in which each of the two components do not necessarily depend on each other and can act in their own way. In contrast, the second comprises synergistic synbiotics in which the

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prebiotic component is specifically intended to support the growth of the accompanying probiotic (Kolida & Gibson 2011).

Given the lack of an updated definition of synbiotic, the International Scientific Association for Probiotics and Prebiotics (ISAPP) is working on a Consensus Statement on the scope of synbiotics' definition, uses, types and health attributes. One concept emerging from this discussion is allowing flexibility of the synbiotic term to be used with combinations of live microbes and selectively utilized substrates, which on their own may not meet the definition of probiotic and prebiotic, but work together when combined to deliver a health benefit through a synbiotic effect.

The most widely studied prebiotics available commercially as synbiotics include inulin, fructooligosaccharides, and galactooligosaccharides. Regarding the probiotic component of synbiotics, we should keep in mind that not all probiotic strains are the same (Sanders ME *et al.*, 2018). The mechanisms of action of some probiotics might be widespread among studied probiotic genera, while others may be unique to specific strains (Hill *et al.*, 2014).

Some foods seem to be nature's approach to designing synbiotics. For example, human breast milk contains both prebiotic oligosaccharides (human milk oligosaccharides) as also delivers potentially beneficial live microbes. However, as ideal as breast milk is, it cannot be considered a synbiotic because the live microbial component of breast milk is not suitably characterized.

In the global marketplace, synbiotics are delivered to consumers in food form or dietary supplements. Synbiotic dietary supplements should be labeled in a manner that enables consumers and healthcare practitioners to determine if evidence supports specific product claims. So checking synbiotic supplement product labels is an appropriate way of learning to identify science-based synbiotics (<https://isappscience.org/for-consumers/infographics/>).

Conditions in which synbiotic treatments have been explored through randomized and placebo-controlled trials include inflammatory bowel diseases (ulcerative colitis and Crohn's disease), diarrhea, irritable bowel syndrome, metabolic syndrome, colon cancer, and kidney and liver diseases (Krumbeck JA *et al.*, 2018).

The World Gastroenterology Organisation supports their benefits as an adjuvant therapy for *Helicobacter pylori* eradication; the treatment of non-alcoholic fatty liver disease by improving the main factors causing the condition; irritable bowel syndrome; and functional constipation in adults (World Gastroenterology Organisation, 2017). In the pediatric population, synbiotics have shown to be effective in gastrointestinal-related conditions [e.g. reducing the duration of diarrhea and hospitalization in children (Yang B *et al.*, 2019)] and in preventing sepsis in full-term newborns (Panigrahi P *et al.*, 2017).

Below, readers will find several articles on the functions and preventive or therapeutic actions of synbiotics in different conditions, alongside science-based advice for identifying high quality synbiotics in the marketplace. You can also stay up-to-date on the latest advances in the gut microbiota field by following Gut Microbiota for Health-related resources (www.gutmicrobiotaforhealth.com and @GMFHx on Twitter).



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A large clinical trial in India finds a synbiotic may help prevent neonatal sepsis

Published on October, 19, 2017 by Paul Enck

Sepsis is a life-threatening condition characterized by systemic inflammation; it is one of the major contributors to neonatal mortality, especially in developing countries. The World Health Organization (WHO) estimates that 1 million deaths per year (10% of all under-five mortality) are due to neonatal sepsis and that 42% of these deaths occur in the first week of life. Although exclusive breastfeeding and chlorhexidine antiseptic interventions (on vaginal areas, newborn skin and the umbilical cord) have been proven to benefit neonatal health in low-resource settings, no prophylactic tool is widely used.

A new community-based, double-blind, placebo-controlled randomized trial, led by Dr. Ira H. Gewolb from the Division of Neonatology at College of Human Medicine at Michigan State University (East Lansing, Michigan, USA), has found that a **synbiotic consisting of a strain of *Lactobacillus plantarum* and fructooligosaccharide may be effective in preventing sepsis in rural Indian newborns**. Synbiotics are combinations of a probiotic -the *Lactobacillus plantarum* strain - with a prebiotic - here the fructooligosaccharide.

The researchers enrolled 4,556 healthy newborns -all of them weighing at least 2,000 g at birth, born at 35 weeks of gestation or later, who were breastfed and had no signs of sepsis or other morbidity- from 149 randomly chosen rural Indian villages and monitored them for 60 days. It is noteworthy that neonatal and infant mortality rates in the studied region are among the highest in India, according to the Department of Health & Family Welfare from the Government of Odisha state.

Infants in the treatment arm (n = 2,278) took a daily dose of the synbiotic (consisting of a capsule containing 10⁹ colony forming units of *Lactobacillus plantarum* ATCC strain 202195 and 150 mg of fructooligosaccharide with 100 mg maltodextrin as excipient) for one week, whereas the placebo group (n = 2,278) took capsules containing only 250 mg of maltodextrin.

Primary outcome was a composite of sepsis (composed of septicaemia, meningitis, culture- negative sepsis, and low respiratory tract infections) or death.



Secondary outcomes were other infections (including diarrhoea, omphalitis, local infections, abscess, and otitis media) and weight gain.

The colonizing ability, tolerance and impact on the stool microbiota of administration of *L. plantarum* ATCC strain 202195 in combination with fructooligosaccharide was previously reported in newborns by the same research group. The probiotic strain was initially isolated from healthy volunteers' stool and when administered to infants colonized their gut successfully and remained there for up to 4 months.

Newborn babies who took the synbiotic had a significantly lower risk of developing sepsis. Just 5.4%

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of the infants who took the synbiotic developed sepsis in their first 2 months of life, compared to 9% of those who received a placebo. The researchers calculated that the reduction of sepsis risk was between 25-50%. Some sepsis cases in newborn babies begin in the gut and the synbiotic may prevent them by either ousting pathogenic microorganisms or stopping commensal ones from entering the bloodstream and causing infections.

Apart from preventing sepsis, **the synbiotic also reduced the risk of infection by Gram-positive bacteria (by 82%), Gram-negative bacteria (by 75%), and pneumonia and other airway-related infections (by 34%).**

Regarding tolerance and safety, the symbiotic was well tolerated and did not cause any harmful side effects.

Only 6 cases of abdominal distention were reported across both groups.

To sum up, this is the first large clinical trial that has found benefits of a symbiotic for sepsis prevention in newborns from a developing country. “We may need to test this in different settings and we are working with the government to do so,” says the first author Dr. Panigrahi. In an article in *The Atlantic*, Ed Yong writes, “Beyond protecting infants... this approach would also reduce the use of antibiotics, and slow the spread of drug-resistant infections. And perhaps best of all, it can be done cheaply. You would need to treat 27 infants to prevent one case of sepsis, and each week-long course costs just one U.S. dollar.”



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Reference:

Panigrahi P, Parida S, Nanda NC, *et al.* A randomized synbiotic trial to prevent sepsis among infants in rural India. *Nature*. 2017. doi: 10.1038/nature23480.



Read the original post online at:

<https://www.gutmicrobiotaforhealth.com/en/large-clinical-trial-india-finds-synbiotic-may-help-prevent-neonatal-sepsis/>

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A synbiotic mixture may have an impact on healthy young children's gut microbiota

Published on May, 3, 2018 by GMFH Editing Team

It has been suggested that the first 3 years of life are a critical period for dietary interventions aimed at gut microbiota modulation for improving child growth and development—the so-called “window of opportunity for microbial modulation”. Contrary to current belief, recent research has found that the gut microbiome of young children and adolescents is different from that of adults. Although the composition and diversity of gut microbiota may change during childhood and adolescence in response to physiological and environmental cues, studies assessing the impact of nutritional interventions with specific mixtures of prebiotics and/or probiotics on healthy toddlers' gut microbiota are scarce.



A new randomized, double-blind and controlled multicenter clinical study, led by Dr Pantipa Chatchatee from the King Chulalongkorn Memorial Hospital in Bangkok (Thailand), **has found that a synbiotic formula supplemented with short-chain galacto-oligosaccharides /long-chain fructo-oligosaccharides and *Bifidobacterium breve* M-16V may modulate healthy toddlers' gut microbiota by increasing levels of *Bifidobacterium*.**

In order to study the impact of nutrition on the development of the fecal microbiota in healthy children, the researchers randomized 129 healthy Thai children aged between 1 and 3 years to receive either the synbiotic formula (n=65) or the control product (n=64) over a period of 12 weeks. Subjects were balanced across the study groups with respect to baseline characteristics.

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The formula for these young children consisted of 0.95 g/100 mL of scGOS/lcFOS (ratio 9:1) and 1.8×10^7 colony-forming units/g of *B. breve* M-16V, administered three times a day, with 210 mL at each serving. Meanwhile, the control group received the same formula without supplementation. Stool samples were used to determine stool characteristics as a measure of safety and tolerance, the composition and metabolic activity of the fecal microbiota (measured as a panel of the fecal pH and several organic acids including acetic, propionic, n-butyric, iso-butyric, n-valeric and iso-valeric acids and lactate), and the level of secretory immunoglobulin A.

Previous research that has investigated the therapeutic effect of this synbiotic mixture in infants has demonstrated its role in reducing the severity of immunoglobulin E-associated atopic dermatitis and preventing delayed colonization by *Bifidobacterium* in infants delivered by C-section.

Stool microbiota at baseline was comparable between both groups, with *Bifidobacterium* as the predominant bacterial member. **The consumption of the synbiotic formula containing scGOS/lcFOS and *B. breve* M-16V led to an increased proportion of *Bifidobacterium* at week 12 compared to baseline,** together with a significant difference (7.48%) in change from baseline at week 12 between the intervention and control groups. Within the active group, the proportion of *Lactobacillus* and *Enterococcus* genera also increased significantly from baseline to week 12.

The consumption of the synbiotic mixture was also accompanied by a more acidic intestinal milieu and led to softer stool consistency at week 6 and week 12 compared to the control group. Lactate and short-chain fatty acids were not affected after 12 weeks of synbiotic formula intake. As for the impact of the synbiotic mixture on mucosal immunity, the level of secretory IgA increased in the active group compared to the control group, although this change did not reach statistical significance.

Some adverse events and a few serious adverse events were detected in both groups, with no difference in incidence and type between the active and control group; they were not considered to be related to the study product.

In conclusion, the results of this study show that a synbiotic formula supplemented with scGOS/lcFOS and *B. breve* M-16V may have a positive influence on the development of the fecal microbiota in healthy toddlers by increasing levels of *Bifidobacterium*, decreasing intestinal pH and driving softer stools. Further studies are needed to better explore exposure to the consumption of synbiotics early in life and the outcomes for health.



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Read the original post online at:

<https://www.gutmicrobiotaforhealth.com/en/a-synbiotic-mixture-may-have-an-impact-on-healthy-young-childrens-gut-microbiota/>

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A synbiotic intervention in c-section-born infants may help emulate the gut environment observed in vaginally-delivered infants

Published on April, 3, 2018 by GMFH Editing Team

It is a well-known fact that caesarean section (c-section) birth is related to an increased risk of both immune and metabolic diseases later in life, possibly through aberrant gut microbiota composition and/or functional diversity. However, little is known about the effect of targeting gut microbiota with prebiotics and probiotics in c-section-born infants.

A new randomized, double-blind, controlled multicentre study, led by Dr. Voranush Chongsrisawat from the King Chulalongkorn Memorial Hospital at the Faculty of Medicine at Chulalongkorn University in Bangkok (Thailand), has found that **supplementation with galacto- and fructo-oligosaccharides and *Bifidobacterium breve* M-16V in c-section-delivered infants helps emulate the gut physiological environment observed in vaginally-born infants.**

The researchers studied the effect of short-chain galacto-oligosaccharides (scGOS), long-chain fructo-oligosaccharides (lcFOS) and *B. breve* M-16V on the gut microbiota of c-section-born infants. With this aim, infants were randomized to receive a standard nonhydrolyzed cow's milk-based formula (control formula; n = 50), or the same formula supplemented with 0.8 g/100 mL scGOS/lcFOS (prebiotic formula; n = 51) or the identical prebiotic formula additionally supplemented with *B. breve* M-16V at a dose of 7.5×10^8 colony forming units/100 mL (synbiotic formula; n = 52) from birth (1-3 days at the latest) until 16 weeks of age. All infants included were mixed-fed and received the study product corresponding to each experimental group in addition to breastfeeding. A reference group of 30 non-randomized infants born vaginally was also included.

Synbiotic supplementation led to a higher proportion of bifidobacteria -total faecal bifidobacteria was the primary outcome- **from day 3/5 until week 8, and a**



reduction of *Enterobacteriaceae* from day 3/5 until week 12, compared to controls. These results show that supplementation with scGOS/lcFOS and *B. breve* M-16V may compensate for the delayed *Bifidobacterium* colonization in c-section-delivered infants. Besides this, **the synbiotic was also able to decrease faecal pH (acidification of the gut) from day 3/5 until week 4, which could be explained by the increased faecal acetate levels.** The authors hypothesized that the reduced abundance of *Enterobacteriaceae* in the synbiotic formula group was likely due to the increase

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of acetate induced by the synbiotic. Both the reduction of *Enterobacteriaceae* and the increase of acetate have been previously reported as markers of a healthy gut ecosystem.

At the end of the study, the proportion of subjects with detectable infant type *Bifidobacterium* species was comparable across all the intervention groups. In the synbiotic group, *B. breve* M-16V was detected 6 weeks post-intervention in 38.7% of the infants.

In conclusion, this study demonstrates that gut microbiota manipulation early in life in c-section-born infants may help emulate the gut physiological environment observed in vaginally-delivered infants.



Supplementation with galacto- and fructo-oligosaccharides and *Bifidobacterium breve* M-16V in c-section-delivered infants helps emulate the gut physiological environment observed in vaginally-born infants.



Reference:

Chua MC, Ben-Amor K, Lay C, *et al*. Effect of synbiotic on the gut microbiota of cesarean delivered infants: a randomized, double-blind, multicenter study. *J Pediatr Gastroenterol Nutr.* 2017; 65(1):102-6. doi: 10.1097/MPG.0000000000001623.



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Human milk oligosaccharides are detectable in serum and may affect maternal metabolism

Published on September, 19, 2019 by GMFH Editing Team

Breast milk has been reported as a multifunctional fluid, which includes human milk oligosaccharides (HMOs) that may influence the development of the gut microbiota and the training of a newborn baby's immune system.

A recent pilot study led by Dr. Mireille van Poppel and colleagues from the University of Graz and BioTechMed-Graz in Austria has revealed that during pregnancy, HMOs are present in maternal serum and show associations with maternal body composition in normal-weight women. These findings suggest these molecules might have systemic implications for both maternal and fetal health during pregnancy.

In an attempt to explore the effects of HMOs on maternal metabolism, Jantscher-Krenn and colleagues from the University of Graz in Austria followed a sample of 87 overweight or obese pregnant women at increased risk of gestational diabetes mellitus (GDM).

All HMOs measured in serum (2'-fucosyllactose, lactodifucotetraose, 3'-sialyllactose, and 3'-sialyllactosamine) increased from early to mid- and late pregnancy.

Furthermore, **researchers found different associations between HMOs in early pregnancy and maternal metabolic outcomes in late pregnancy**, with 3'-sialyllactose and 3'-sialyllactosamine in serum positively associated with changes in fasting glucose at 24 and 32 weeks. In addition, lactodifucotetraose was positively associated with changes in insulin and insulin resistance (HOMA-index) at 24 weeks.

The secretor status of pregnant women (secretor positive vs. secretor negative) did not have an influence on the serum levels of all studied HMOs.

Although a previous study has shown that a certain type of HMO improves glucose tolerance and insulin sensitivity in diet-induced obese mice, this is the first time HMOs have been linked to glucose homeostasis in humans.

The authors also developed a statistical model that featured several parameters—fasting glucose, pre-pregnancy body mass index, gestational weight gain, age, parity, smoking, history of macrosomia and 3'-sialyllactose in early pregnancy—to predict the development of GDM. **When compared with fasting glucose, the serum levels of 3'-sialyllactose in early pregnancy were better predictors of GDM development in pregnancy.**

These results suggest that **HMOs may contribute to explaining how pregnancy-induced metabolic changes can drive an increased risk of GDM in overweight and obese pregnant women.**

On the whole, this new research highlights a novel role for HMOs in regulating maternal glucose metabolism beyond their known biological functions. Although the causal contribution of HMOs to GDM in overweight and obese pregnant women deserves further research, these findings highlight the relevance of HMOs for maternal metabolism and as a predictive biomarker for predicting GDM.



Reference:

Jantscher-Krenn E, Treichler C, Brandl W, *et al.* The association of human milk oligosaccharides with glucose metabolism in overweight and obese pregnant women. *Am J Clin Nutr.* 2019. doi: 10.1093/ajcn/nqz202.



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SELECTED CONTENT

An expert panel helps end users identify high quality probiotics

Published on June, 10, 2019 by Mary Ellen Sanders

Many consumers and healthcare providers are aware that certain probiotics may be beneficial for health. But they sometimes have difficulty identifying high quality products in the marketplace.

What is a high quality probiotic product? It contains microbial strains that are properly identified, characterized and quantified, it meets specifications for purity, it is safe for its intended use, and it is manufactured in compliance with Good Manufacturing Practices appropriate for the category of the product. Further, to be called 'probiotic', the product must have been shown in controlled human trials to confer a health benefit.

A panel I chair under the auspices of the United States Pharmacopeia, recently collaborated on an expert opinion paper that **summarizes recommendations to companies producing probiotics, outlining proper standards in quality manufacturing processes and ways to communicate quality to end users.**

We recommend that probiotic producers undergo third-party evaluations to certify both probiotic quality and label accuracy. This use of a third party provides unbiased confirmation of product quality to end-users. Our paper describes the steps necessary for setting up the third-party certification of a probiotic product, in a process that is followed by established certification bodies:

- Submission of an application to the certification body.
- Submission of documents regarding facility statistics, a standard operating procedures index, an analytical methods index, a quality manual index, a hazard analysis, a critical control point plan and an allergen control plan.
- Quality management systems audit.
- Documentation review.
- Verification of all testing methods.
- Corrective or preventative actions.
- Formal issuance of the certification for the product.



These steps will assure the consumer about quality in manufacturing. To improve transparency to the end-user, some organizations offering third-party certification services authorize the use of a logo or seal that makes it clear that the specific probiotic has been manufactured following stringent conditions.

It should be noted that this process is separate from assessments of the strength of evidence supporting any health claims for a probiotic product.

The panel also calls for publicly available quality standards and methods for identifying the probiotic strain, quantifying viable probiotic cells throughout production and distribution, and ensuring purity. The definition of a probiotic implies that it must be a defined entity to allow for appropriate identification to the strain level, so the panel recommends quantifying specific strains in multi-strain probiotic products. Some of the emerging methodologies that may be useful for quality assessment thus include whole genome sequencing of the bacteria to confirm the probiotic identity.

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As both consumers and healthcare providers struggle to know which probiotics are backed by evidence, we recommend that the probiotic products available on the market conform to labeling standards advanced by the World Health Organization and the World Gastroenterology Organization:

- Genus, species and strain names.
- Statement of quantity (using colony forming units or another validated measure) of live/active micro-organisms through the use-by date. (Levels of live probiotics should be provided through the 'best by' or 'use by' date and not time of manufacture).
- Use by date.
- Statement of benefit: although it is not required, when present, it must be supported by a human study showing the benefit at the dose delivered in the product.
- Proper storage conditions.
- Company contact information.

Information can be found at these links on how to read a label on a probiotic food supplement sold in the European Union and the United States.

Overall, this new expert panel document aims to provide ways of showing probiotic quality standards to consumers so they can recognize high-quality products. Currently, this goes beyond regulatory requirements in many jurisdictions. But undergoing unbiased third-party certification is a straightforward way for probiotic companies to improve transparency when it comes to probiotic product quality.



What is a high quality probiotic product? It contains microbial strains that are properly identified, characterized and quantified. Further, to be called 'probiotic', the product must have been shown in controlled human trials to confer a health benefit.



Mary Ellen Sanders is a consultant in the area of probiotic microbiology, with special expertise on paths to scientific substantiation of probiotic product label claims. Dr. Sanders served as the founding president of the International Scientific Association for Probiotics and Prebiotics (www.isappscience.org) and is currently the organization's Director of Scientific Affairs/ Executive Officer.



Reference:

Jackson SA, Schoeni JL, Vegge C, *et al.* Improving end-user trust in the quality of commercial probiotic products. *Front Microbiol.* 2019; 10:739. doi: 10.3389/fmicb.2019.00739.



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