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INSIGHTS FOR HEALTHCARE PROFESSIONALS

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The importance of **the first 1000 days** and gut colonization

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The first 1000 days: a period of development

The first 1000 days, from conception to around a child's third birthday, represent a unique window of opportunity to lay the foundation for a child's future health.[1-3] This period is of crucial importance for the healthy development of the gut, the gut microbiome, the immune system, and the brain.[4]

There is a lot of crosstalk between the gut microbiome[5] and the immune system as the gastrointestinal (GI) tract contains 70–80% of the body's immune cells and hosts a permanent microbial ecosystem.[6] This ecosystem is collectively called the "gut microbiome" and is used to indicate the collection of over 1000 different species of bacteria, viruses, archea, fungi, and protozoa populating the GI tract, particularly the colon.[3] The gut microbiome and its development in early life are essential factors in establishing and maintaining a proper gut function, which influence the maturation of the immune system.[7-10]

The immune system is a complex network of specialized organs, cells, and molecules that helps to protect us from diseases caused by microorganisms and toxins.

During the first 1000 days of life, the immune system needs to mature and be trained for appropriate immune responses.[11] Establishing and maintaining a stable and symbiotic microbial community after birth can have a significant effect on the development of the innate and adaptive immune systems.[3,12,13] The early life gut microbiome has also been linked to brain development. Further understanding of the complexity of the microbiome–gut–brain relationship and the role of nutrition to promote normal brain development in early life is important [Figure 1].[14]

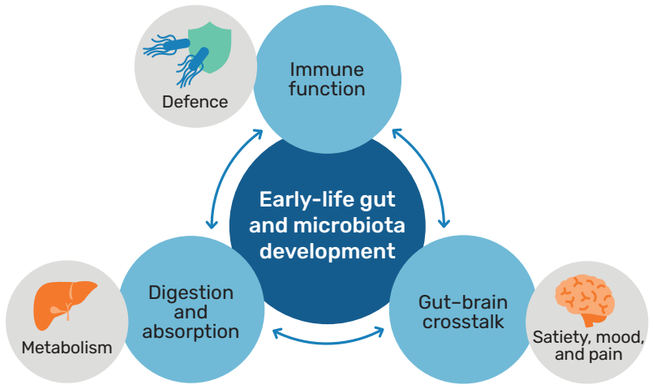

Figure 1. The gut is our largest immune organ[15,16].

The establishment of **the gut microbiome is a process over time**

The colonization of the intestinal microbiome is a dynamic process during infancy, shaped by environmental factors.[17] It slowly develops, reaching a mature state at around three years of age.[4,18]

The amount and types of microbes change over time [Figure 2], following the steps mentioned below. Immediately after birth, the infant gut is rich in oxygen, which offers a favorable habitat for facultative anaerobic microorganisms such as *Staphylococcus spp., Streptococcus spp.,* and *Enterobacter spp.*[20,21] These species rapidly transform the microbiome environment, which becomes a place for taxa that thrive in strictly anaerobic conditions, such as *Clostridium, Bacteroides, Eubacterium,* and *Bifidobacterium spp.*[20]

After one week of life, *Bifidobacterium, Bacteroides,* and *Clostridium* are detected in the feces, and at this time, in breastfed infants, *Bifidobacterium spp.* become dominant.[7] The introduction of more complex solid foods promotes the colonization of the infant gut with an increasing number and diversity of bacteria.[18] By approximately three years of age, the diversity and complexity of the gut microbiota stabilizes and resembles that of an adult.[18]

The westernized lifestyle impacts exposure to microbes due to improved hygiene standards during early childhood, which leads to a hypersensitive immune response to normally harmless exposures.[4,22] This is caused by the reduced richness and diversity of the gut microbiome and subsequent reduced training of the immune system.[4,22,23] Both microbes and food play a role in infection prevention, mucosal health, gut function, and immune maturation early in life.[24]

The gut microbiome impacts **short- and long-term health outcomes**

The development and maintenance of a balanced microbial community after birth is widely recognized to play an essential role in contributing to short- and long-term health and disease.[7] Many factors are known to positively or negatively influence the gut microbiota, for example, breastfeeding is a key driver in establishing a healthy gut microbiome that is rich in *Bifodobacterium spp.* Read more about the factors impacting the gut microbiota in the next chapters.

The gut microbiome is widely recognized to contribute to an infant's short- and long-term health.

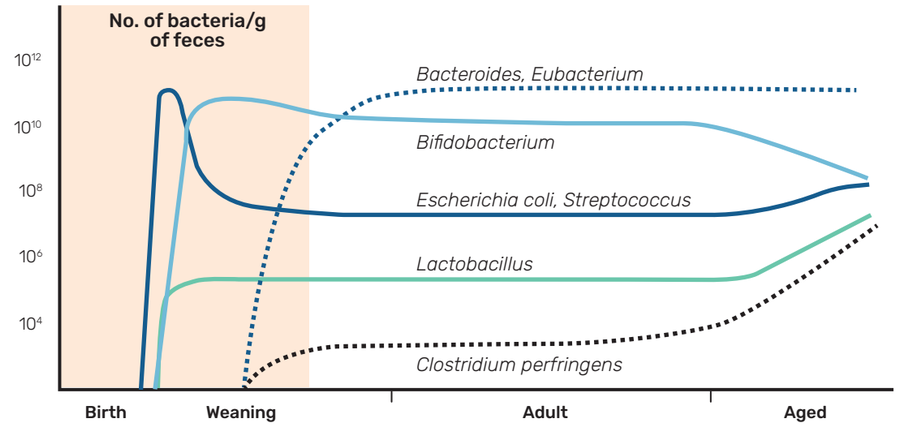

Figure 2. The amount and types of microbes change over time[19]

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Factors affecting the **gut microbiota development**

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Several factors impact **the development and colonization of the gut microbiota**

Pregnant mothers' gut microbiota greatly contributes to infant's gut colonization immediately after birth. Therefore, nutrition during pregnancy is very important as it affects the composition of microbiota that gets transferred to the infant. Mode of delivery has a major influence on the gut microbiota development in early life. Infants born vaginally have their guts first colonized by the mother's gut and vaginal microbiota. In contrast, infants delivered via Cesarean section (C-section), are first exposed to the mother's skin and hospital environment, and thus, their microbiota do not resemble the mother's vaginal and gut microbiota.[1,2]

After birth, the mode of feeding, that is, breastmilk versus formula milk, has a major impact on the process of colonization and microbiota composition. The gut of a healthy breastfed infant is typically dominated by bacteria of the *Bifidobacterium* species. These species are first transmitted from the mother during birth and via the breastmilk. Formula-fed infants develop a more adult-like microbiota composition, with higher overall early bacterial diversity.[3]

Recent evidence indicates that lifestyle changes owing to modernization, such as increased rates of birth by C-section, increased early use of antibiotics, and other pharmaceuticals (e.g. proton pump inhibitors and non-steroidal anti-inflammatory drugs), a westernized diet and the associated development of obesity, excessive hygiene practices, exposure to air pollution, and activity patterns, directly and indirectly impact the formation of a diverse microbiota.[1–9]

A recent double-blind, placebo-controlled trial in daycare children 3–5 years of age, investigated the consequence of exposure to microbially diverse sand versus microbially poor sand. It concluded that daily exposure to microbial diversity is associated with immune regulatory responses and could therefore contribute to a child's immune health [Figure 1].[10]

Many factors can impact the development and colonization of the gut microbiota[1–9,11]

Mode of delivery: C-section versus vaginal
Term: Full-term versus preterm delivery
Mode of feeding: Breastfeeding versus formula feeding
Increased early use of antibiotics use of other medicines (e.g. proton pump inhibitors and non-steroidal anti-inflammatory drugs)
Westernized diet and the associated development of excessive hygiene practices (e.g. low exposure to microbes)
Exposure to air pollution
Home environment and household pets such as dogs
Activity patterns

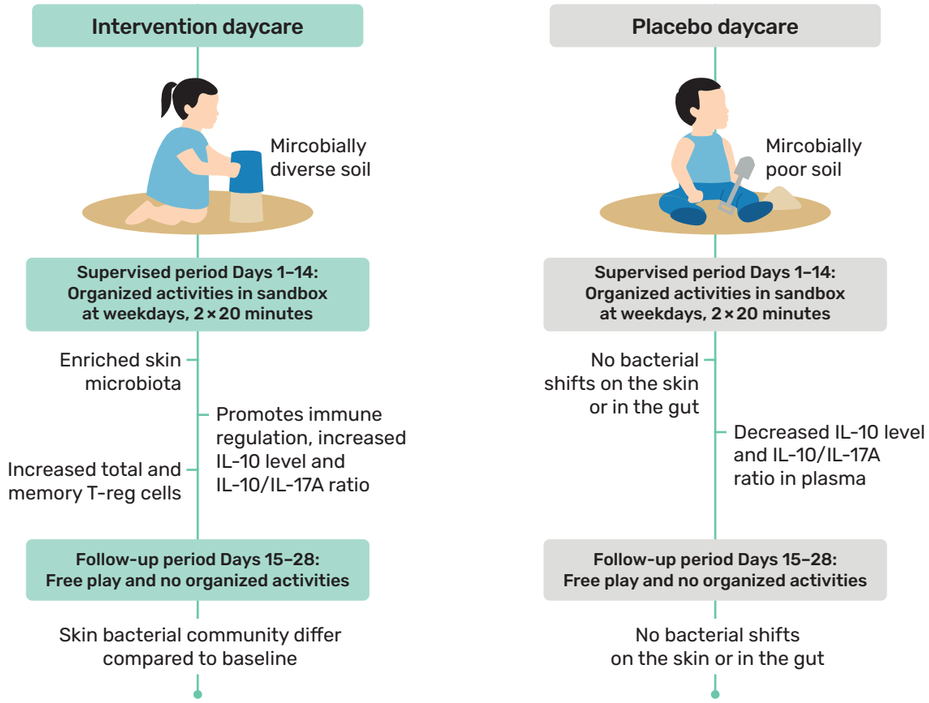


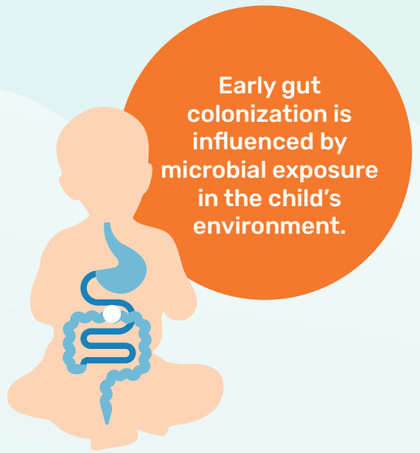
Figure 1. Exposure of children to microbially diverse soil was associated with the enrichment of skin microbiota and promotion of immune regulatory responses. Adapted from [10].

Potential consequences of **dysbiosis in early life**

Aberrations in the composition and function of the microbiota, known as dysbiosis, are characterized by a state of imbalanced proportions and functions of commensal, beneficial, and potentially harmful bacteria, largely caused by environmental influences and exposures. In infancy, dysbiosis is often characterized by a lower presence of *Bifidobacterium* and higher presence of *Enterobacteriaceae*.[5]

A growing body of evidence suggests that dysbiosis in infancy may not only be associated with health problems in early life, such as an increased risk of infections and colic pain and discomfort, but may also increase the risk of childhood diseases that can persist to adulthood, such as allergy, autoimmune diseases, irritable bowel syndrome, autism, obesity, diabetes, and psychological disorders including anxiety and depression.[6,7,12–18]

Therefore, it is important to further increase the understanding on how the microbiota develops and how nutrition can play a role in modulating the gut microbiota, particularly in case of gut microbiota dysbiosis. The next chapters will describe the impact of antibiotic use and C-section as well as potential ways to influence gut microbiota.



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C-section and its consequences on the gut microbiota and health outcomes

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C-section: **a growing health concern**

Nowadays, Cesarean sections (C-section) have become increasingly common in both developed and developing countries. When medically necessary, a C-section can effectively prevent maternal and neonatal mortality. Yet, today 3 out of 10 infants are born by C-section (many elective) in Europe, and it can reach higher rates in certain geographies.[1]

Delayed gut microbiota colonization in infants born via C-section

Bifidobacterium and *Bacteroides* are suggested as microbial biomarkers of vaginally born and breastfed infants.[2] Multiple studies from several geographical locations indicate delayed colonization by these "keystone colonizers" in infants delivered via C-section [Figure 1].

Several studies suggest that when the pattern of gut microbial colonization is disturbed during the first days of life and persists over the first year, the compromised microbiota represents a non-negligible risk factor for immune-related diseases in childhood and later in life.[3] The delayed colonization occurs within the critical window of development during the first 1000 days of life, which is a sensitive period because the disruption in establishment of early life microbiota may have lifelong health consequences.[4] Notably, a depletion of *Bifidobacterium* during the first three months of life has been identified as one presumed microbiome parameter that contributes to an increased risk of respiratory infections, atopic diseases, and obesity.[5–8] The increased risk of childhood infections upon birth via C-section is persistent until five years of age, as demonstrated in a large worldwide birth cohort study.[9] The infections were predominantly respiratory, gastrointestinal, and viral in nature.[9]

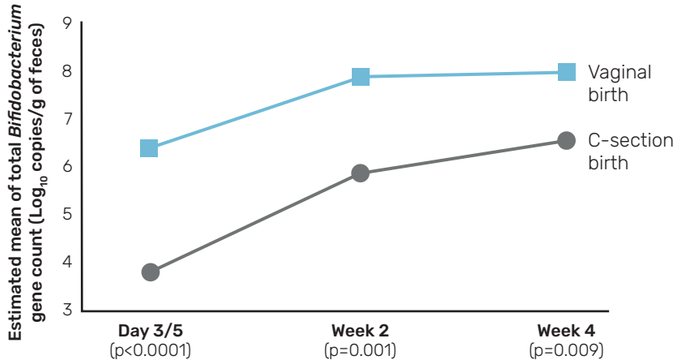

Figure 1. Delayed *Bifidobacterium* colonization in infants born via C-section compared to those born vaginally.[10]

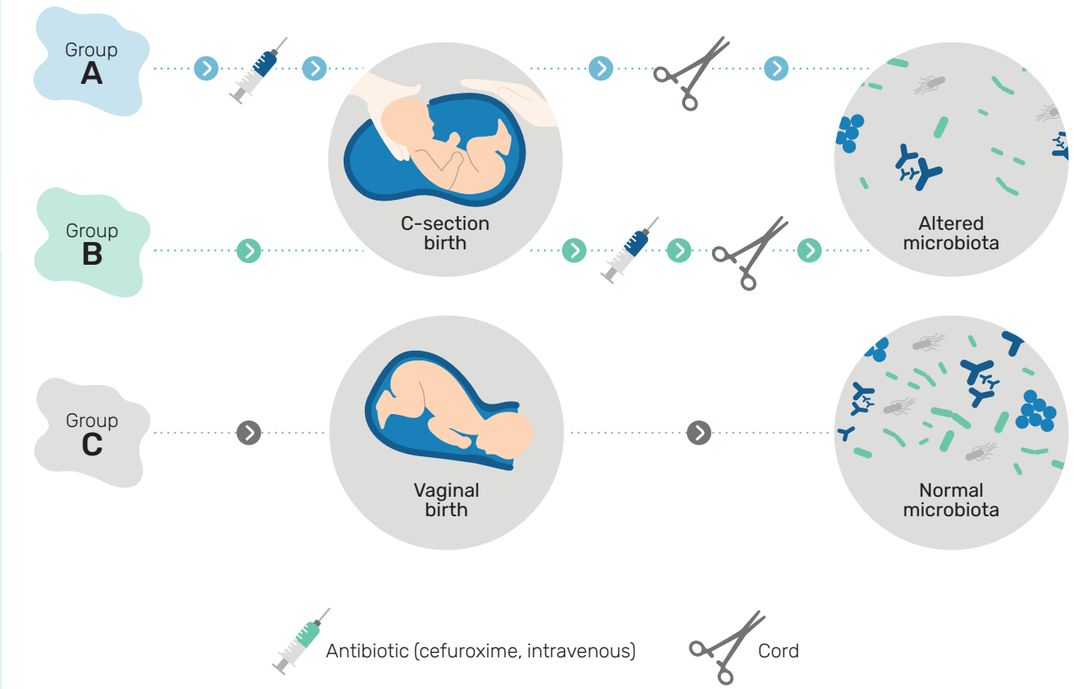

Figure 2. Effect of C-section on early-life gut microbiota development independent of maternal antibiotic exposure (cefuroxime) before or after cord clamping.[11]

C-section or maternal antibiotics – **what is causing the observed dysbiosis?**

As standard clinical practice, intrapartum antibiotic prophylaxis (IAP) is usually administered to prevent post–C-section maternal infection. IAP has been suggested as a factor that determines the compromised microbiome in infants born by C-section. However, a recent study looked at the impact of the timing of maternal antibiotic administration during C-section and showed that major changes occurred in the microbiome of all infants born via C-section independently of whether the antibiotic was given before skin incision or after cord clamping[11] [Figure 2]. Maternal antibiotic administration prior to C-section did not further compromise the gut microbiota composition. This indicates that C-section delivery is a strong contributor to the microbial disbalances observed in comparison to IAP administration.

Infants born by C-section miss out on some important "keystone colonizers," putting the infant at a heightened risk of developing immune-related diseases in childhood and later in life.

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Early-life exposure to antibiotics:
Impact and consequences on the gut microbiota

Tim de Meij has been working as a consultant pediatric gastroenterologist at Amsterdam UMC since 2011. His main clinical focus includes the care for children with inflammatory bowel disease. Tim has a keen interest in translational research, focusing on microbiology and metabolomics in gastrointestinal inflammatory diseases. He completed his thesis "Microbiota and flatography in pediatric gastrointestinal disease" in 2017. His current focus lies on the development of novel, microbiota-related diagnostic biomarkers for gut inflammation, including necrotizing enterocolitis, inflammatory bowel disease, and sepsis. He incorporates these themes in his scientific work.

Increased prescription of **antibiotics in early life**

Antibiotics are very effective against a wide range of bacterial infections and have saved the lives of many patients. Antibiotics are commonly prescribed medication in infants and children due to the high prevalence of infections in early life.[1] Also, antibiotics are often prescribed to term and late preterm neonates with suspected early-onset sepsis, which could be reduced by only prescribing the neonates with pathogenic blood cultures.[2] Moreover, adjustment of guidelines over the past decades has resulted in an increased use of intrapartum and postnatal antibiotics in infants. In some regions, the prescription of antibiotics is especially high. It was observed that, in a US cohort, 70% of the infants received at least one prescription of antibiotics in the first year of life.[3] Another study showed that 39.7% infants in five European countries received it at least once in the first year of life.[4]

Impact of antibiotics on the **early life gut microbiota**

There is however also a downside of the exposure to antibiotics. Several studies showed that antibiotics have been strongly associated with gut microbiota disturbances in both infants and children.[5,6] In comparison with adults, antibiotic exposure in early life strongly impacts the microbiota composition, since the developing gut microbiota is more susceptible to disruptions due to the low diversity and high instability in early life.[7,8]

A prospective cohort in Finland showed that even a short course of antibiotics can have a long-term effect on the gut microbiome colonization.[6] Upon antibiotic exposure, infant-type *Bifidobacteria* are decreased whereas adult-type *Clostridia* are increased.[6] After cessation of antibiotic use, Bifidobacterial levels are restored; however, full recovery can take up to 6 months [Figure 1].[6]

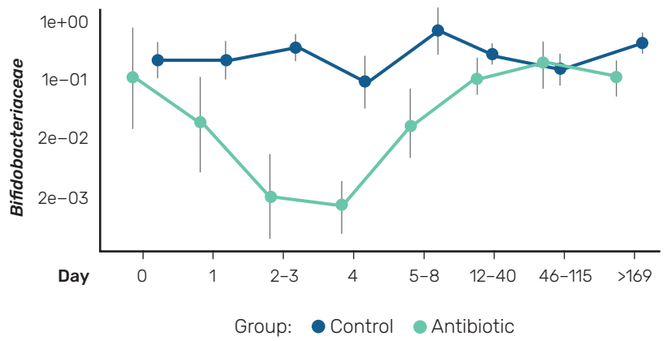

Figure 1. Effects of antibiotic use on the gut microbiota persist after cessation.[6] Recovery of Bifidobacterial levels can take up to 6 months. Evidence suggest that especially early antibiotic exposure may be detrimental, due to the early disruption of the gut microbiota colonization and its consequences on short- and long-term health.[6]

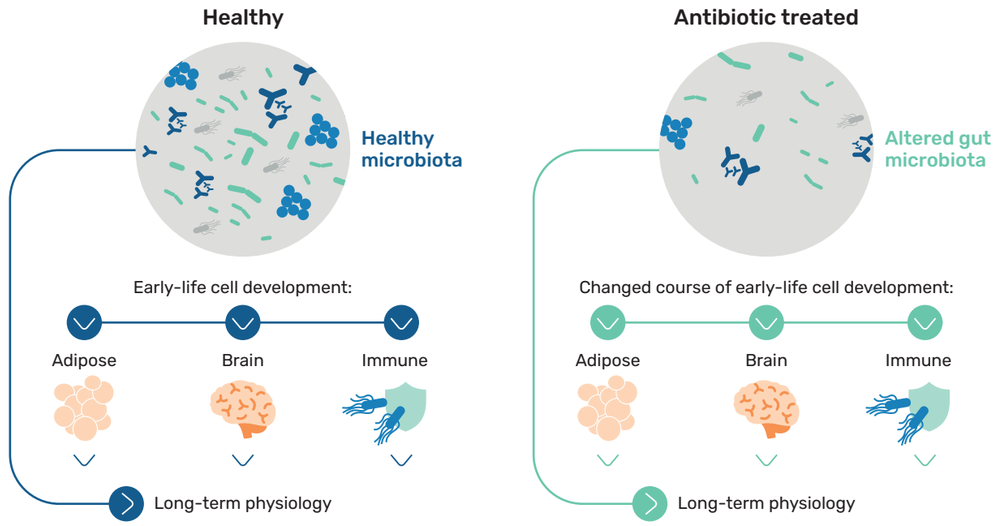

Figure 2. Early antibiotics-related gut microbiota disruptions affect the development of several body systems and may consequently impact long-term physiology. Adapted from [7].

Consequences **beyond the gut microbiota**

Early disruption of the gut microbiota development by antibiotics may negatively affect short- and long-term health outcomes.[6] Early antibiotic use is associated with an increased risk of immune-related disorders and an increased susceptibility to develop non-communicable diseases, like asthma, obesity, and gastrointestinal diseases like inflammatory bowel diseases.[6,9–12] For example, a large cohort study indicated that infants exposed to antibiotics in the first two years of life had an increased likelihood of developing asthma and allergic rhinitis, which was highly dose-dependent, especially when receiving multiple courses of antibiotics.[13] Another study showed an increased risk of food allergy, specifically milk and egg allergy, in infants exposed to antibiotics in the first six months of life.[14] In a large cohort of preterm infants, the duration of antibiotic exposure was strongly associated with severe health events on the short term, like necrotizing enterocolitis and sepsis.[15] These findings underline the need for the judicious use of antibiotics in early childhood and the need for developing strategies to protect against antibiotic-related dysbiosis.

Next to effects seen on immune-related disorders, other developmental pathways might be affected by antibiotic-related gut microbiota disruptions as the gut microbiota influences the development of many other body systems and organs, such as adipose tissue and the brain via the so-called "gut-brain axis." Exposure to antibiotics is associated with inferior cognitive, behavioral, and emotional outcomes beyond childhood[16] and metabolic-related disorders that may be present up to adulthood, such as malnutrition and obesity [Figure 2].[9–11]

Several studies have shown promising effects of nutritional strategies, including formula with pre-, pro-, and synbiotics, to restore the compromised gut microbiota caused by factors such as Cesarean section and early-life antibiotic exposure to avoid further health consequences.

Early antibiotics are life-saving, but the development of novel strategies is needed to protect the developing microbiota and improve short- and long-term health outcomes.

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Opportunities to rebalance the gut microbiota dysbiosis with **nutritional interventions**

Prof. Cai Wei is a Distinguished Professor and Doctoral Supervisor of Shanghai Jiao Tong University, Director of Shanghai Institute for Pediatric Research, and Dean of Shanghai Key Laboratory of Pediatric Digestion and Nutrition.

The role of nutrition on gut microbiota dysbiosis

Early-life nutrition greatly enables a healthy immune system and gut microbiota development.[1] In infants with risk factors for gut dysbiosis, such as infants born via Cesarean section (C-section) or who received antibiotics, it is important to provide additional nutrients that can restore the gut microbiota dysbiosis.

While breastmilk remains the best source of nutrition for infants, for mothers who are unable or unwilling to (fully) breastfeed, infant formula supplemented with prebiotics, probiotics, or synbiotics has been proposed as a nutritional solution to selectively stimulate growth and activity of the gut microbiota, thereby impacting the gut microbiota colonization as well as gut and immune system maturation.[2–9]

Prebiotics and probiotics – definitions and health outcomes

Prebiotics are frequently added to infant formula to mimic the effects of human milk oligosaccharides and promote the growth of *Bifidobacteria* and *Lactobacilli*. Prebiotics short-chain galacto-oligosaccharide and long chain fructo-oligosaccharides (scGOS/lcFOS) are selectively utilized by host microorganisms, conferring a health benefit. The specific scGOS/lcFOS (9:1) mixture has shown that the gut microbiota of infants receiving scGOS/lcFOS was more similar to infants fed breastmilk than infants fed standard formula without scGOS/lcFOS, including a lower sum of clinically relevant pathogens after the intervention[10–15] and a significantly lower number of infections[16] with lasting effects on infections and antibiotic treatment until 2 years of age.[15]

Probiotics are live microorganisms that can supplement the bacterial populations in the infant gut and reverse the dysbiosis.[5] *Bifidobacterium breve* M-16V is from the family of bifidobacterial species, commonly found in the gut of breastfed infants.[17,18]

Synbiotics to compensate for the **delayed colonization in infants born by C-section**

Synbiotics are a mixture of prebiotics and probiotics that can restore the gut microbiota disbalance induced by C-section or antibiotic use. A synbiotic is defined as "a mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit to the host".[9]

The specific synbiotic mixture of prebiotic oligosaccharides scGOS/lcFOS (9:1) with *B. breve* M-16V has shown an increased beneficial effect over individual components in pre-clinical models.[19]

Chua and colleagues conducted a study aimed to restore the gut microbiota and support immune system development in infants born via C-section receiving a synbiotic mixture of prebiotic oligosaccharides scGOS/lcFOS (9:1) with *B. breve* M-16V. They demonstrated that the specific synbiotic mixture compensated the delayed colonization of *Bifidobacterium* in infants born by elective C-section from the first days of life, bringing the composition close to vaginally born infants [Figure 1].[20]

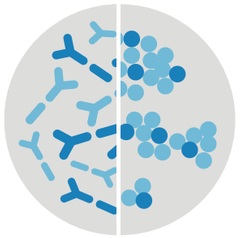
Over the course of the 16 weeks of intervention, the synbiotics supplementation was accompanied with the development of indigenous infant, type *Bifidobacterium* species such as *Bifidobacterium breve*, *Bifidobacterium longum,* and *Bifidobacterium bifidum*. This indicates that supplementation with a unique probiotic strain, *B. breve* M16V, did not impair the development of other indigenous bifidobacterial communities over time. Additionally, this synbiotic modulation of the gut microbiota was accompanied by acidic gut physiological conditions as observed in vaginally born infants, reflecting the rapid settlement of these infant bacterial species.[20]

This was confirmed in another clinical trial testing the same synbiotic concept.[21] This trial demonstrated that the level of *Bacteroides*, another important infant gut bacterial species, is restored in C-section–born infants to level similar to that found in vaginally born infants. This restoration of the gut microbiota composition lasted even beyond the synbiotic intervention indicating that early restoration with this specific synbiotic concept can have long-term effects.[21] Lastly, it was demonstrated that potential pathogenic bacteria were decreased upon intervention with this synbiotic mixture in C-section infants.[22]

Several factors can impact the development and colonization of the gut microbiota in early life. C-section–born and antibiotic use are potential risk factors for gut microbiota dysbiosis. Studies with synbiotics show their ability to restore the gut microbiota colonization pattern. Further research is needed to determine the potential benefits on short- and long-term health.

Synbiotics[8,9]

Synbiotics are a mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confer a health benefit to the host.



Food for good bacteria + good bacteria

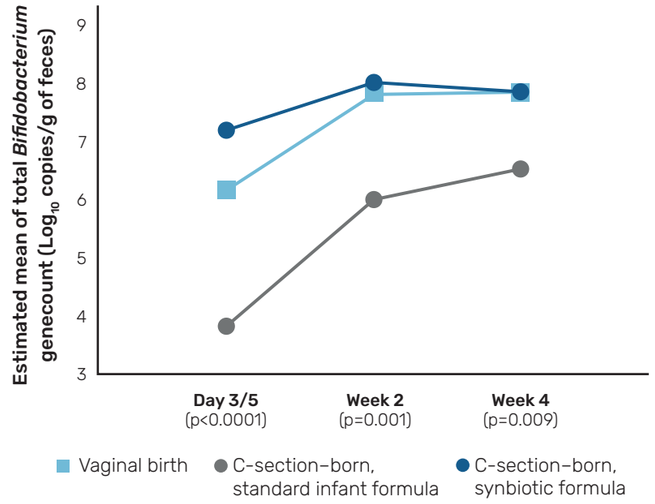


Figure 1. The gut microbiota colonization in C-section–born infants has been shown to be significantly different from that in vaginally born infants.[20]

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