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The infant gut microbiota: a narrative review about development and external determinants

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Review

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Abstract

This narrative review examines the development of the infant gut microbiota during the early months of life, highlighting the impact of delivery mode and feeding practices on microbial colonization and overall infant health. The search was conducted using the Virtual Health Library and PubMed databases, with the descriptors "gut microbiota" combined with "breastfeeding" (BF) and "infant formula." After screening, 18 articles were selected for final analysis. Findings indicate that cesarean section reduces initial gut microbial diversity by 30%–50% and decreases *Bifidobacterium* colonization, while increasing the abundance of *Enterobacteriaceae* and *Clostridium*. In contrast, exclusive BF supports a more favorable microbial profile, enriched in bifidobacteria, and contributes to immune system maturation. The literature also highlights the importance of other genera, including *Lactobacillus*, *Veillonella*, and *Firmicutes*, in regulating inflammation, producing short-chain fatty acids, and protecting against pathogens. Supporting vaginal birth and exclusive BF emerges as a key strategy to promote a more resilient and health-promoting gut microbiota during infancy.

Introduction

Breast milk is considered the gold standard for infant nutrition because it is essential for proper growth and development. Exclusive breastfeeding (BF) is recommended up to six months of age, as breast milk has a complex composition that makes it unique. It contains various biologically active components, such as immunoglobulins, growth hormones, oligosaccharides, and the infant's own microbiota, which play crucial roles in intestinal homeostasis, immunity, and development.[1–3]

In the first weeks of life, a healthy gut microbiota is characterized by limited bacterial diversity. Initially, the colonies resemble those in the mother's gut when birth occurs by vaginal delivery (VD). In infants fed breast milk, bifidobacteria predominate.[1] In contrast, the gut microbiota of infants born by cesarean section (CS) is comparable to that following antibiotic ingestion, with persistent early-life disturbances characterized by reduced *Bacteroides* colonization and slower microbial community development.[4] Although CS, when indicated for medical reasons, can reduce or avoid risks to mother and child, it is important to emphasize that CS rates between 10% and 15% are associated with lower maternal and infant mortality.[5,6] However, the global CS rate is 21.1%, with Brazil ranking second in the world at 55.7%, after the Dominican Republic (58.1%). In private hospitals, this rate can reach up to 90%.[7] According to the Pan American Health Organization, the CS rate has risen from around 7% in 1990 to 21% currently, with a further increase expected over the next decade that could reach 28.5% globally by 2030, with significant regional variations.[8]

Other changes associated with CS include reduced microbial diversity, delayed colonization by *Bacteroides* and *Bifidobacterium spp.*, and the development of *Clostridium spp.*[9–12] Although CS is necessary in certain circumstances, it has been associated with the development of immunological diseases, a phenomenon that can be explained by altered maturation of the gut microbiota.[13–16]

The infant gut microbiota develops through two key transitional phases. The first occurs immediately after birth during BF, resulting in a gut microbiota dominated mainly by *Bifidobacterium*. The second phase begins with the introduction of solid foods, leading to a more complex microbiota similar to that of adults, primarily composed of *Bacteroides* and *Firmicutes*.[17] *Clostridium difficile* is widespread in the gut microbiota, present in nearly half of infants under one month old and accounting for up to 30% of the infant microbiota within the first six months of life.[18] Although this bacterium is associated with diarrhea in adults, it remains unclear whether colonization with *C. difficile* triggers intestinal dysbiosis in infants or if pre-existing dysbiosis favors colonization by this microorganism.[18] The importance of gut microbiota composition for infant health is therefore evident.[11,13]

BF directly affects the newborn's microbiota and provides both short- and long-term health benefits into adulthood.[19] Modulating the gut microbiota through breast milk may reduce the risk of allergic disease by taking advantage of the "window of opportunity" in the first months of

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life to influence long-term health outcomes.[20,21] Early-life colonization with a diverse gut microbiota promotes immune tolerance by supporting the development of regulatory T cells and limiting IgE production and pro-inflammatory iNKT cell activation, thereby reducing the risk of allergic disease.[20] Several factors, such as delivery method and feeding type, significantly affect the composition of the infant's gut microbiota. In recent years, infant formula consumption has increased due to positive claims on product labels and aggressive marketing that encourages caregivers to substitute formula for breast milk, leading to the misconception that it is as effective as or even better than breast milk.[22]

With this in mind, the aim of this study is to provide an overview of the development of the microbial profile of the infant gut in the first months of life and to highlight the influence of factors such as mode of delivery and feeding to understand their impact on infant health.

Methods

We reviewed the literature to understand the initial development of the early gut microbiota. The process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure 1). We searched the Virtual Health Library and PubMed databases using the descriptors "gut microbiota" combined with "breastfeeding" and "infant feeding" with Boolean operators (AND/OR). We applied a temporal filter for publications from the last 10 years and a language filter (Portuguese, English, and Spanish) to ensure the evidence was current.

We then identified, selected, and analyzed relevant studies. The selection process was conducted in three rigorous steps: (1) initial screening by title, (2) review of abstracts, and (3) reading of full texts. After removing duplicates using the EndNote Web Reference Manager, we applied the exclusion criterion to studies that did not match the central theme, such as animal studies, assessments of gut microbiota as an exposure factor, and studies involving preterm infants, infants with certain diseases, or infants older than six months. Finally, 18 articles were included in the final analysis (see Figure 1).

The data extracted from the selected studies were summarized in a table and figure, including authorship, year of publication, country of origin, objectives, methodology, sample characteristics, and main findings. Data were extracted and reviewed by two authors (TBC and SP).

Results and discussion

As summarized in Table 1, the included studies were distributed across various countries, each represented to different extents. China contributed three publications,[23–25] as did Japan.[26] Italy,[27,28] Mongolia,[29,30] the United States,[4,31] and the Netherlands[32,33] each contributed two articles. Spain,[11] Armenia and Georgia,[34] Belgium,[35] the Netherlands,[36] Canada,[37] and Thailand[38] each had one publication.

Regarding sample size, the study with the fewest participants was by Kongnum *et al.*,[38] which included only six ($n = 6$) full-term infants, limiting the generalizability of the results. In contrast, the study with the largest number of participants was conducted by Borewicz *et al.*,[33] which analyzed two different cohorts in the Netherlands – the Bingo and Koala studies – and thus had a more representative sample and greater statistical power, with 443 full-term infants.

Among the most important exposures studied, the mode of delivery stands out for its role in shaping the infant's gut microbiota and its impact on infant health.[4,11,23–26,30,32,34,35,37,38] The relationship between the type of infant feeding – exclusive BF, mixed feeding, or formula feeding – has also been extensively studied.[4,23–28,30–38]

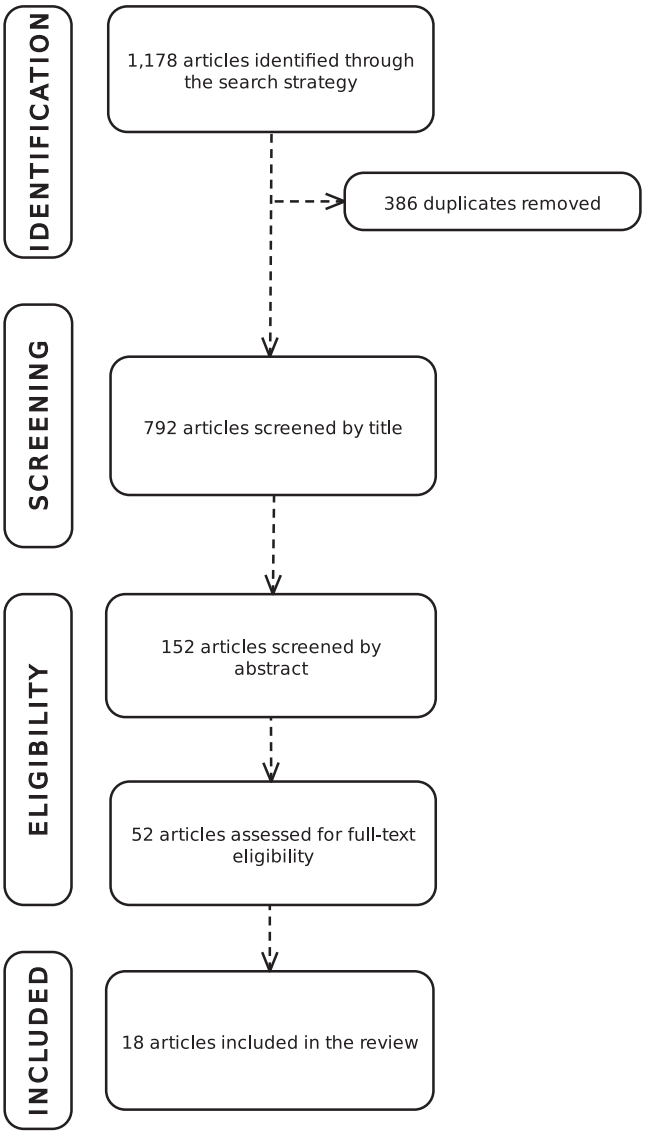


Figure 1. Flowchart of the search strategy.

Influential highlighted microorganisms

In addition, the selected studies identified several microorganisms relevant to the intestinal microbiota of infants. We emphasize the presence of *Bifidobacterium* spp.,[23,25,29,32,34,36,37,39] *Escherichia* spp.,[11,23,28,29,32,33,37] *Clostridium* spp.,[11,24,25,29,31,34,36,37] *Lactobacillus* spp.,[23,24,26,27,34,38] and *Bacteroides* spp.,[11,27–29,31,34] Additionally, representatives of *Firmicutes*,[11,24,25,28,31,33,37] *Staphylococcus* spp.,[11,32–34] *Enterococcus*,[11,23,25,30–33] and *Streptococcus* spp.[23,31–34,36] are repeatedly reported, reflecting the diverse microbial composition of the infant gut.

Chronology and development of the gut microbiota

Analysis of the chronological and critical development of the infant gut microbiota reveals several milestones within the first 180 days

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Table 1. Summary of the studies included in the literature review

Author, year and country	Objective and population	Methods	Results
Azad *et al*., 2013[37]Canada	To characterize the gut microbiota of healthy Canadian infants and describe the influence of CS and infant formula. $n = 24$ full-term babies	This study included a subgroup of breastfeeding women from the Canadian Healthy Infant Longitudinal Development (CHILD) birth cohort. Mode of delivery was obtained from medical records, and mothers were asked to report their infant's diet and medication use. At 4 months of age, stool samples were collected and the composition of the microbiota was characterized by high-throughput DNA sequencing.	Predominant bacterial phyla: Actinobacteria (median 36.4%), mainly the genus *Bifidobacterium*; Firmicutes (median 43.8%) with multiple genera; significant negative correlation between Actinobacteria and Firmicutes ($r = -0.92$, $p < 0.001$). Proteobacteria (median of 7.4%) present in all infants; and Bacteroidetes found in 37.5% of the population, absent in CS infants. Infants born by CS had a lower abundance of *Escherichia–Shigella* ($p < 0.001$) and absence of *Bacteroides* ($p = 0.02$); non-breastfed infants had a higher abundance of *Peptostreptococcaceae* ($p = 0.002$) and *Verrucomicrobiaceae* (genus *Akkermansia,* $p = 0.001$); prevalence of *Clostridioides difficile* was significantly lower in exclusively breastfed infants (20% vs. 71% in non-breastfed infants, $p = 0.01$).
Bokulich *et al*., 2017[4] United States	Characterization of the profile of microbial development in the first 2 years of life. $n = 43$ infants in a cohort	The samples were collected from birth to the age of 3 years. Especially in the first year, the stool was collected 12–24 hours after birth and monthly thereafter. DNA extractions from biological samples and PCR analyzes of the V4 region of the 16S RNA genes were performed.	Antibiotics, CS and infant formula alter microbiota patterns and development in the first two years of life.
Borewicz *et al*., 2020[32] Holland	Investigation of the relationships between the concentrations of selected oligosaccharides (HMOs) in breast milk, infant feces and the composition of the fecal microbiota in healthy breastfed infants. $n = 24$ mothers and full-term infants in a cohort	The samples were taken at 2, 6 and 12 weeks of age. The bacterial DNA from the feces was extracted and then the resulting models were amplified by PCR of the V4 region of the 16S RNA genes. The HMOs in the feces were quantified by high-performance liquid chromatography or high-performance anion exchange chromatography.	Redundancy analysis (RDA) showed that infant age, sex, place of birth, mode of delivery, secretory status and concentrations of HMOs in breast milk influenced the composition of the microbiota, with an explained variation of 56.58%. HMO intake correlated with infant age and microbial composition, showing higher abundance of Bifidobacterium OTUs and other groups such as *Parabacteroides*, *Escherichia-Shigella* and *Bacteroides* with increased HMO intake. Significant correlations were observed between HMO concentrations in milk and the relative abundance of bacterial OTUs in feces, especially *Staphylococcus*, *Streptococcus*, *Actinomyces* and *Enterococcus*. The profile of HMOs in breast milk varied with time of lactation, with mean concentrations of HMOs decreasing, except for 3 FL and LNFP III, which increased with time. At 3 months of age, fecal HMO concentrations were very low/undetectable, resulting in less clear overall correlations between bifidobacteria and fecal HMOs.
Borewicz *et al*., 2019[33] Holland	The colonization patterns of commercially breastfed and formula-fed infants with and without probiotics were compared, including a group of mixed-breastfed infants. $n = 443$ full-term infants from 2 cohorts, named BINGO and KOALA	Samples were collected at 2, 6 and 12 weeks of age. Bacterial DNA from the feces was extracted and, subsequently, the resulting models were amplified by PCR of the V4 region of the 16S RNA genes.	Five main phyla were identified: Actinobacteria, Bacteroidetes, Firmicutes, Proteobacteria and Verrucomicrobia. Abundant genera: *Bifidobacterium*, *Bacteroides*, *Streptococcus*, *Escherichia-Shigella*, and unclassified genus *Enterobacteriaceae*. BINGO cohort: *Bifidobacterium* abundance increased with age in breastfed infants ($p = 0.01$), but fluctuated in formula-fed (FF) and mixed-fed (MF) infants. KOALA cohort: Formula-fed infants had lower *Bifidobacterium abundance* compared to breastfed infants ($p = 0.00078$). At six weeks, FF infants in BINGO had higher (non-significant) abundance of *Bifidobacterium*; in KOALA, FF infants had lower abundance ($p < 0.05$).

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Table 1. (*Continued*)

Author, year and country	Objective and population	Methods	Results
			Formula feeding has increased significantly ($p < 0.05$) *the relative abundance of Akkermansia, Enterococcus, Peptostreptococcaceae incertae sedis* and *Erysipelotrichaceae incertae sedis*, and significantly decreased the relative abundance of *Staphylococcus* and *Haemophilus*, compared to those on breastfeed. The type of feeding can explain 4.5% of the residual variation in microbiota composition at week 6 and increased to 5.9% at week 12, when adjusting the model for the type of delivery.
Corvaglia *et al*., 2016[27] Italy	To evaluate the effect of intrapartum antibiotic prophylaxis (IAP) for *group B Streptococcus* (GBS) on the gut microbiota in healthy full-term infants, also exploring the influence of feeding type. $n = 84$ healthy full-term infants whose mothers had been screened for (GBS) at the end of gestation.	They were divided into 2 groups: infants born to GBS-positive mothers who received PIA *vs* controls. Samples were collected at 7 and 30 days of age. DNA was extracted and the microbial groups selected were quantified. (group*Lactobacillus* spp., *Bifidobacterium* spp. *e Bacteroides fragilis*) was performed by real-time PCR.	The use of IAP significantly reduced the *Bifidobacterium spp. count.* at 7 days of life (median of 6.01 log CFU/g in the IAP group *vs* 7.80 in the control group, $p = 0.000$), but there was no difference at 30 days (8.41 *vs* 8.39, $p = 0.842$). The count of *Lactobacillus spp.* and *B. fragilis* showed no significant difference between the groups at any evaluation point. Hierarchical regression analysis indicated that the type of diet was significantly associated with the increase of *Lactobacillus spp.*, with higher counts in exclusively breastfed infants, regardless of IAP use. At 7 days, the *Bifidobacterium spp.* was higher in infants who did not receive IAP and were exclusively breastfed ($R^2 = 0.301$). At 30 days, the *Bifidobacterium spp.* was not influenced by IAP or type of diet.
Guo *et al*., 2020[23] China	To reveal whether breastfeeding could restore the gut microbiota (IM) established in CS relative to VD and decrease the risk of infections early in life. $n = 41$ babies	Fecal samples were collected at six different times (1, 3 and 7 days and 1, 3 and 6 months after birth). The children were divided into 4 groups according to the type of delivery (CS or VD delivery) and feeding pattern (breastfeeding (B) or infant formula (F)). DNA was extracted, and then the V3–V4 region of the 16S rDNA gene was amplified.	In VD infants, *Bifidobacterium* was less abundant, and the delay in the establishment of GM may be partially restored by breastfeeding. Breastfeeding significantly reduced the incidence of respiratory infections and diarrhea in neonates of both groups (VD and CS) ($p < 0.001$). Diet was the primary factor influencing gut microbiota composition in the first 6 months of life ($p = 0.004$). CS neonates showed greater IM diversity (3.18 ± 0.68) compared to VD (3.01 ± 1.51), with no statistical significance. *Bifidobacterium* was almost twice as abundant in the meconium of VD neonates (20.70% ± 20.01) compared to CS, while CS neonates accumulated more *Escherichia/Shigella, Enterococcus, Streptococcus, Burkholderia, Acinetobacter, Lactobacillus* and *Ralstonia*. IM evolved from Cluster 1, dominated by *Escherichia*/*Shigella*, in the first week of life, to Clusters 2 and 3, with higher abundance of *Bifidobacterium* between D7 and M1, especially in breastfed neonates. *Pseudomonas*, dominant in meconium, decreased drastically on the third day in breastfed neonates ($p = 0.004$ VD_B and $p = 0.028$ CS_B). Breastfed CS neonates showed greater similarity in IM with VD neonates (increase from 0.18 to 0.52) compared to formula-fed neonates; CS_F had higher abundance of unsorted taxa and lower *Bifidobacterium load*, while VP_B showed the opposite pattern.

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Table 1. (*Continued*)

Kongnum *et al*., 2020[38] Thailand	To understand the role of breastfeeding in the colonization and succession of bifidobacteria in the infant intestine, longitudinally. $n = 6$ healthy infants born at term.	Fecal samples were collected from all infants from 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 4 months, and 5 months postpartum. In addition, breast milk and feces profiles were compared in three mother-infant pairs. The samples were subjected to DNA extraction and preparation for nestedPCR-DGGE analysis (electrophoresis gel to a denaturation gradient) to determine bifidobacterial diversity.	Exclusively breastfed infants (BF-V and BF-C) had higher *Bifidobacterium* abundance (36%–70% and 32%–47%) and mean stool counts of 9.22 and 9.20 log cells/g over 5 months, while lactobacilli predominated in infants fed formula (FF-V and FF-C) or combined feeding (CF-V and CF-C), with peaks of 9.31, 9.27, and 9.24 Log $cells_{10}$/g stool. Formula supplemented with *B. animalis subsp. lactis* increased bifidobacteria in FF-V (8.82 to 9.45 log cells/g). Breastfed or mixed-fed infants had a higher diversity of bifidobacteria (49–55 bands), with species such as *B. breve, B. bifidum, and B. longum* stable for 5 months, while species in formula-fed infants were more transient. Breast milk was a crucial source of bifidobacteria such as *B. longum and B. infantis*, ensuring stable colonization.
Lewis *et* al., 2017[34] Armenia and Georgia	To evaluate the possible influences on infant gut microbiota through a longitudinal study in cohorts of breastfed infants from neighboring countries, focusing on environmental and community differences that may impact microbial colonization. $n = 53$ Armenian infants and 11 Georgian infants on exclusive breastfeeding	Fecal samples were collected at 3 time points: 1 week of life, 1 month of life, and 3 months of life. DNA was extracted, and then the V4 region of the 16S rRNA gene was amplified by PCR.	Infant origin explained 8.4% of gut microbiota variation ($r^2 = 0.084$; $p = 0.001$). Armenian infants had higher abundances of *Enterobacteriaceae*, *Streptococcus*, *Bacteroides*, *Clostridium*, and *B. pseudocatenulatum* ($p < 0.05$), while Georgian infants showed no significant increase in bifidobacteria. The delivery method contributed with 3.1% of the variation ($p = 0.001$), and infants born by VD had higher levels of *B. pseudocatenulatum* ($p = 0.03$), *Enterobacteriaceae* ($p = 0.01$) and *Streptococcus* ($p = 0.008$) compared to those born by CS. Maternal secretory status explained 1.6% of the variation ($p = 0.066$), with infants of secretory mothers showing a greater increase in bifidobacteria up to the 90th day. Between days 7 and 90, there was an increase in *B. breve*, *B. longum subsp. infantis* and lactobacilli ($p = 0.004$; 0.039; and 9.29×10^{-5}, respectively), while *Staphylococcus* and *Planococcaceae* decreased ($p = 3.18 \times 10^{-8}$; 4.86×10^{-5}).
Liu *et al*., 2019[24] China	To determine the individual and combined impacts of mode of delivery, feeding pattern, and postnatal antibiotic exposure on the initial establishment of the infant gut microbiome. $n = 120$ babies	Fecal samples were collected 6 weeks after delivery. Clinical information was collected from medical records and questionnaires. The V3-V4 regions of the 16S rRNA gene were analyzed by *Illumina sequencing*, and clinical information was obtained from medical records and questionnaires.	A total of 3,367,929 bacterial sequences were identified in 120 fecal samples from infants, representing 8 phyla and 147 genera. The most abundant phyla were Firmicutes (44.9%), *Proteobacteria* (22.7%), *Actinobacteria* (18.7%) and Bacteroidetes (13.2%). The 10 most abundant genera included *Bifidobacterium* (17.3%), *Clostridium sensu stricto* 1 (12.8%), and *Klebsiella* (10.7%). Infants born by CS had a significantly different microbial structure from those born by VD, with a lower abundance of *Bifidobacterium* and a higher abundance of *Lactobacillus*, *Veillonella* and *Klebsiella* ($p = 0.044$). There were no significant differences in alpha diversity between exclusively breastfed and mixed-fed infants, but among those born by CS, the microbiota of exclusively breastfed infants was more similar to that of those born by VD ($p < 0.01$). Antibiotic exposure had no significant impact on gut microbiota composition, except for the genus *Lachnoclostridium*, which was lower in exposed infants ($p = 0.006$).

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Table 1. (*Continued*)

Author, year and country	Objective and population	Methods	Results
Ma *et al.*, 2020[29] Mongolia	Detect the gut microbiota in infants fed exclusively with breast milk or a certain type of formula for more than 4 months after birth. $n = 91$ full-term NB	All infants were evaluated at 40 days, 3 months and 6 months of age. The infants were divided into 3 groups: breastfeeding (30 infants), formula A (30 infants), or formula B (31 infants) exclusively for more than 4 months after birth. DNA was extracted, and then the V4 region of the 16S rRNA gene was amplified by PCR.	*Bifidobacterium* represented the most predominant genus and Enterobacteriaceae the second, in all groups at all times. *Bifidobacterium* represented 46.2%, 41.4% and 29.9% in the breastfed group, 32.2%, 35.3% and 31.7% in the formula A group and 33.0%, 39.8% and 39.0% in the formula B group at 40 days, 3 months and 6 months of age, respectively. At 40 days, *Bacteroides* ($p = 0.012$) and *Bifidobacterium* ($p = 0.015$) were significantly higher in the breastfed group than in the group fed formula A. Alpha diversity increased significantly in the group breastfed at 6 months ($p = 0.0038$), while in the formula A group it decreased at 3 months ($p = 0.0029$). Beta diversity increased in the breastfed group ($p < 0.0001$) and in the formula A and B groups at 6 months ($p = 0.0167$ and $p = 0$). *Bifidobacterium* was predominant in all groups. At 40 days, *Veillonella and Clostridioides* were lower in the breastfed group ($p = 0.002$ and $p = 0.007$). At 3 months, significant differences were observed for *Lachnospiraceae and Clostridioides* ($p = 0.001$ to $p = 0.015$). Bacteroides*abundance* was negatively correlated with CS and *Enterococcus* was positively correlated with antibiotic use in infants. The relative abundance of *Enterococcus* was positively correlated with the use of antibiotics in infants.
Ma *et al.*, 2022[30] Mongolia	Compare the gut microbiota of healthy infants based on specific interactions, by birth and feeding types. $n = 62$ healthy babies	Clinical data were collected from the mothers and infants. 59 stool samples were collected at 40 days, 60 samples at 3 months, and 53 samples at 6 months of age. DNA was extracted, and then the V4 region of the 16S rRNA gene was amplified by PCR.	*Bifidobacterium* represented the most predominant genus in all groups, at all times evaluated, and *Enterobacteriaceae was later observed*. At 40 days, α diversity was lower in breastfed (BF) infants compared to formula-fed infants (IF), with a significant difference between VD-BF and VD-IF ($p = 0.05$). At 3 months, diversity was significantly lower in the CS-BF group compared to the other groups ($p = 0.005$ to 4.0E-05), but there was no difference at 6 months. β diversity increased over the first 6 months, being higher in the RV groups at 40 days ($p = 0.0008$ to 9.93E-16). At 3 months, β diversity was lower in the VD-BF and CS-FI groups compared to the VD-FI and CS-BF groups. *Bifidobacterium* was the predominant genus in all groups, being more abundant in babies breastfed at 40 days, especially in the CS-BF group. At 3 months, the abundance of *Enterococcus* was higher in the formula-fed infants, while at 6 months, the abundance of *Bacteroides* was higher in the VD-BF group compared to the CS-FI.
Martin *et* al., 2016[35] Belgium	Describe the dynamics of early colonization during the first 6 months of life and identify factors that may lead to changes in gut microbiota composition early in life. $n = 108$ babies	After delivery, fecal samples from neonates were collected at the following times: first defecation, 2 days after the first defecation, 1 week after birth, 1, 3 and 6 months after birth and 1 week after the start of weaning. The composition and functionality of the microbiota was characterized by the measurement of 33 different bacterial taxa by qPCR/RT qPCR.	Bacterial DNA was detected in most of the meconium samples, suggesting that bacterial exposure occurs in the uterus. VD-born had significantly higher bacterial meconium counts than CS-born (8.47 *vs*. 7.76 Log^{10} cells/g feces, first defecation sample, $p = 0.024$). *B. bifidum* were higher in infants born by VD during the first week of life.

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Table 1. (*Continued*)

			Exclusive breastfeeding for the first 3 months, in contrast to mixed feeding, was associated with a higher *Bifidobacterium count* (10.07 Log^{10} cells/g of stool *vs.* 9.49 log^{10} cells/g of feces, respectively).
Mazzola *et al* 2016[28]Italy	Use whole genome sequencing in combination with qPCR to thoroughly examine the impact of maternal IAP on faecal microbiota composition during 1 month of life, as well as breastfeeding. $n = 26$ infants	The infants belonged to one of 4 groups: 1) LM-C, breastfed infants born to GBS-negative mothers, not receiving IAP before/at delivery (control); 2) LM-PIA, breastfed infants born to GBS-positive mothers treated with PIA; 3) BF-C, infants with mixed feeding born to GBS-negative mothers (control); 4) BF-PIA, BF infants born to GBS-positive mothers, treated with IAP. Feces were collected on the 7th and 30th days of life. DNA was extracted, and then the V4 region of the 16S rRNA gene was amplified by PCR.	At 7 days, microbiota diversity was significantly lower in BF-IAP infants, with lower presence of *Actinobacteria* (absent in BF-IAP and present in 17% in BF-C). The abundance *of Proteobacteria* was higher in the BF-IAP group ($p < 0.062$), especially in the genus *Escherichia* (52% in BF-IAP versus 14% in BF-C). In addition, *Bifidobacterium* was not detected in BF-IAP at 7 days, while it represented 16% of the microbiota in BF-C ($p = 0.001$). At 30 days, *Bifidobacterium* levels increased in the BF-IAP group, but still dominated *Enterobacteriaceae*. PCoA analysis revealed clear separation between the groups at day 7, but the microbiomes became more uniform by day 30. In the formula-fed infant group (MF-IAP), the diversity was similar, but the microbiota composition showed differences, with a higher abundance of Proteobacteria and Firmicutes in the MF-IAP compared to the MF-C. Over time, the differences decreased, but the greater presence of *Bacteroides* and *Bifidobacterium still prevailed* in the MF-C group. When comparing BF-IAP and MF-IAP, the BF-IAP group had lower diversity, with a dominance of Proteobacteria and absence of *Bifidobacterium* at 7 days. However, at 30 days, there was an increase in *Bifidobacterium* populations in BF-IAP (6%), similar to the MF-IAP group (6%). The q-PCR analysis showed lower numbers of *Bifidobacterium* in the BF-IAP infants at 7 days, but these increased significantly until day 30.
Selma-Royo *et al*., 2020[11] Spain	To investigate the influence of birth-related factors, including the place and type of delivery, on early colonization during the first month of life and on infant growth during the first 18 months. $n = 180$ babies born in hospital and home birth	Clinical and biological collections were performed at birth, 7 days and 1 month of life. DNA was extracted and then the V4 region of the 16S rRNA gene was amplified by PCR.	Hospital-born infants had higher richness ($p = 0.002$) and microbiological diversity ($p = 0.072$) than those born at home. The mode of birth also impacted the microbiota, with babies born by CS showing greater diversity ($p = 0.001$) and richness ($p = 0.031$) microbiological compared to those born by VD delivery. The fecal microbiota of the neonates was dominated by Proteobacteria, followed by Firmicutes and Actinobacteria. Hospital-born infants showed higher abundances of *Finegoldia*, *Clostridioides* and *Klebsiella* ($p < 0.001$), while home-born infants had higher abundances of *Staphylococcus* and *Enterococcus* ($p < 0.001$). Infants born by VD, especially those born at home, had a higher diversity of *Bifidobacterium* ($p < 0.001$). In terms of weight and BMI, infants born by CS had higher BMI and weight/height *z*-scores at 12 months compared to those born by VD or at home ($p < 0.001$). Those born by VD had a higher relative abundance of the *phyla Bacteroidetes* ($p = 0.035$) and Firmicutes ($p = 0.035$), including the genera *Bacteroides* and *Escherichia/Shigella.* The relative abundance of the genus *Bifidobacterium* was higher in vaginal deliveries, at 7 ($p < 0.001$) and 31 days ($p = 0.001$), when compared to CS births. In addition, these harbored a higher relative abundance of the genus *Clostridium sensu stricto*.

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Table 1. (*Continued*)

Author, year and country	Objective and population	Methods	Results
Timmerman *et al.*, 2017[36] Netherlands	To determine the development of the infant gut microbiota in the first 12 weeks of life. $n = 8$ babies.	After stool collections, DNA was extracted, and then the V3-V6 region of the 16S rRNA gene was amplified by PCR.	PCA analysis revealed that variables such as individuality, time, and type of feeding explained 59.5% of the variation in microbiota composition, with individuality explaining 46.5% of this variation. The qPCR analysis identified pathogens potentially present in the gastrointestinal microbiota, such as *C. perfringens* and *C. difficile*, with the presence of *S. pneumoniae* and *H. parainfluenzae* in all infants. *C. difficil*and appeared mainly in formula-fed infants or in those breastfed with supplemental formula after 11 weeks. *Bifidobacterium dentium* was identified in greater presence and in greater relative abundance in formula-fed infants compared to those who were breastfed.
Wang *et al.*, 2015[31] United States	To test the hypothesis that the fecal bacterial genera of breastfed and formula-fed infants differ and that HMOs modulate the microbiota of breastfed infants. $n = 19$ babies	Mothers of infants were recruited for the study between the 3rd trimester of pregnancy and 1st month after delivery. The infant formula was delivered to mothers who wanted it, while still pregnant. DNA was extracted and then the V1–V3 region of the 16S rRNA gene was amplified by PCR.	*Bifidobacterium* accounted for >50% of the total sequences in breastfed or formula-fed infants, with no difference between the two groups. Breastfed infants had a higher relative abundance of Bacteroidetes, while formula-fed infants had a higher amount of Firmicutes ($p < 0.05$). Pyrosequencing *analysis of* the V1–V3 regions of the 16S rRNA gene resulted in 321,822 usable sequences, with an average of 10,734 sequences per sample. The fecal microbial structure of BF infants was significantly different from that of FF infants ($p = 0.005$), as shown by PCoA and dbRDA analysis. The phylum Actinobacteria was the most abundant (~53%), with no significant differences between the BF and FF groups. Breastfed infants had a higher relative abundance of Bacteroidetes, while formula-fed infants had a higher abundance of Firmicutes ($p < 0.05$). The relative abundance of the predominant genera, such as *Bacteroides*, was higher in BF babies, while genera such as *Clostridium XVIII*, *Lachnospiraceaeincertaesedis* and *Haemophilus* were lower in BF babies ($p < 0.05$). *Bifidobacterium* represented more than 50% of the sequences in both groups, with no significant differences. No significant differences in microbial diversity were observed between the breastfeeding and FF groups, according to the observed OTUs indexes, Chao 1 and ACE estimators, and the Shannon and Simpson reciprocal indexes. In breastfeeding infants, the relative abundance of *Enterococcus* was positively correlated with *Bifidobacterium*, *Streptococcus,* and *Veillonella*, but negatively correlated with *Bacteroides* and *Clostridium XVIII.* In the FF group, only negative correlations were observed between *Bifidobacterium* and *Clostridium XVIII* and between *Veillonella* and *Klebsiella*.
Wu *et al.*, 2022[25] China	To determine how mode of delivery and feeding pattern influence the construction of infant gut microbiota and variation in fecal microbial metabolites of a birth cohort. $n = 61$ full-term babies	Fecal samples collected at 4 time points: day 0, day 7, month 1 and month 3. DNA was extracted, and then the V3–V4 region of the 16S rRNA gene was amplified by PCR.	The CS group on breastfeeding had a higher relative abundance of Firmicutes on day 0, compared to the VD group. At 3 months, the VB group showed a lower

Table 1. (*Continued*)

	abundance of *Enterococcaceae* compared to the CS group in breastfeeding. At 3 months, *Blautia* was more abundant in the VD on breastfeeding and CS on breastfeeding groups, while *Enterococcus* was less abundant in the VD group compared to the CS group on breastfeeding. The variation of Firmicutes, Bacteroidetes, Actinobacteria and Proteobacteria over time was more pronounced in the VD and VD groups in breastfeeding, with increases or fluctuations at different time points. The relative abundance of Firmicutes in the CS group with mixed feeding was significantly higher than in the breastfeeding vaginal delivery group. At 3 months of age, the VD group in breastfeeding had a significantly lower relative abundance of *Enterococcaceae* than the CS group with mixed feeding. There were no significant differences between the groups for the levels of acetate, butyrate and propionate at other measurement times.

of life that provide insight into microbial succession, as distinct changes occur in the first months and different patterns emerge at each developmental stage (Figure 2). The key findings highlight the predominant bacteria during this period.

In the first few days – especially during the first week – vaginally delivered (VD) infants have higher levels of *Bacteroidales* (16% compared to 2.4% in CS) and *Enterobacteriales* (35% compared to 4.4%), while *Lactobacillales* (61%) and *Bacillales* (23%) predominate in infants born by CS.[26]

After 30 days, *Bifidobacterium* colonization predominates in breastfed infants, accounting for up to 70 % of the microbiota, while higher proportions of *Enterococcus* and *Clostridium* are found in formula-fed infants.[29,38]

After 90 days, the gut microbiota continues to show distinct patterns based on birth type and feeding method. In breastfed infants, *Bifidobacterium* predominates, with increased levels of *B. breve* and *B. longum subsp. infantis* ($p < 0.05$) and lower levels of *Enterococcaceae* ($p < 0.01$), especially in infants born by VD.[23,25,34] In contrast, infants fed artificial formula have lower levels of *Bifidobacterium* ($p < 0.05$) and a higher incidence of Enterococcus and *Clostridioides*,[30] with these differences being more pronounced in infants born by CS.[24]

Kongnum *et al.* (2020)[38] observed that *Bifidobacterium* remained stable (36–70) in breastfed infants at five months of age, with species such as *B. breve* showing persistent colonization, in contrast to the fluctuations seen in formula-fed infants. After six months (180 days), the divergence in bacterial diversity becomes more pronounced: breastfed infants have a greater abundance of *Bacteroidetes* ($p < 0.0001$), while CS is associated with a lower abundance of *Bacteroides* ($p = 0.035$) and a higher presence of *Clostridium sensu stricto*.[11]

According to Ma *et al.* (2020), differentiation of the microbiota is established by six months of age, with breastfed infants showing higher alpha diversity ($p = 0.0038$) and greater abundance of *Bacteroides* ($p = 0.012$), while formula-fed infants show a stronger association with *Veillonella* ($p = 0.002$) and *Clostridioides* ($p = 0.007$). Selma-Royo *et al.*[11] add that CS at this stage is associated with lower abundance of *Bacteroides* ($p = 0.035$) and increased *Clostridium sensu stricto*, highlighting the lasting influence of the type of feeding. Both studies suggest that the microbiota begins its transition to an adult-like profile at this stage, although significant differences remain depending on feeding type and mode of delivery.

Figure 2 shows the timeline of bacterial colonization during the first six months of life. According to recent literature, in breastfed infants, *Bifidobacterium* (especially *B. breve* and *B. longum subsp. infantis*) predominates and microbial colonization remains stable over time, whereas in formula-fed infants, greater microbial turnover occurs, with a clear presence of *Enterococcus* and *Clostridioides*.

Mode of delivery and feeding practices influence the gut microbiota

The results confirm the importance of *Bifidobacterium spp.* as the most abundant genus in the feces of breastfed infants, with significantly higher levels compared to formula-fed infants.[29,40] This profile is highly beneficial for infant health, as the presence of *Bifidobacterium spp.* promoted by BF is associated with positive modulation of the immune system, including reduced inflammatory markers in the gut and promotion of a balanced immune response.[41,42] According to Henrick *et al.*,[41] abundant intestinal

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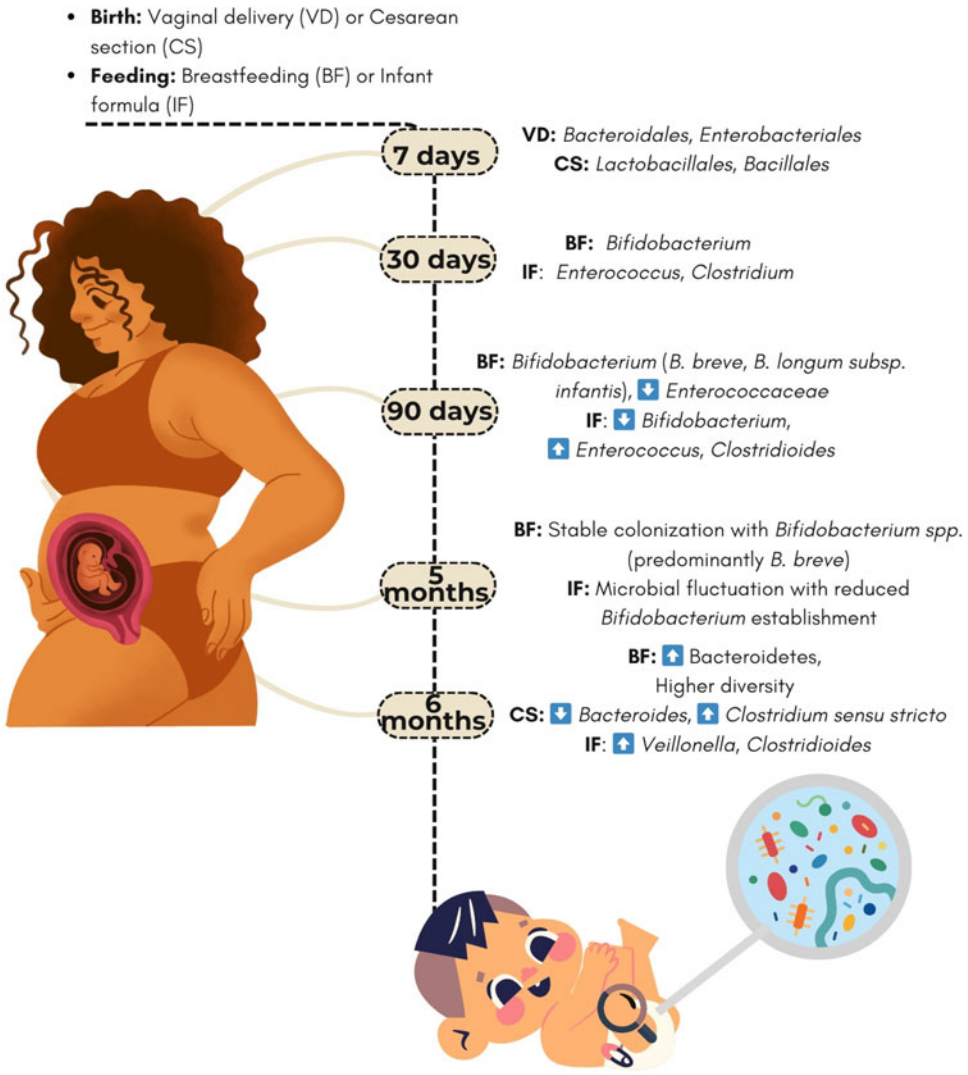


Figure 2. Timeline of bacterial colonization during the first six months of life. (Source: the authors).

bifidobacteria in infants support immune regulation through Tregs and anti-inflammatory cytokines, while low abundance is associated with pro-inflammatory cytokines and immune activation.

The data support the importance attributed in the literature to the genera *Lactobacillus* and *Bifidobacterium* as the most widespread beneficial bacteria that play a crucial role in regulating the infant gut microbiota, exerting antibacterial effects and inhibiting colonization by pathogenic microorganisms.[43] As shown in Figure 2, the mode of delivery also influences this colonization: VD favors *Bacteroidales* and *Enterobacteriales*, while cesarean section is associated with *Lactobacillales* and *Bacillales* in the first days of life.

Studies indicate that the presence of Lactobacillus in feces varies depending on the type of infant formula provided, as many formulas are fortified with probiotics to mimic the benefits of breast milk.[44] Additionally, probiotic lactic acid strains isolated from infant feces – *Lactobacillus gasseri* FWJL-4, *Lactobacillus plantarum* Fjias-5, and *Lactobacillus rhamnosus* FSJ-13 – exhibit anti-inflammatory and antioxidant effects by activating the Nrf2/HO-1 signaling pathway in macrophages.[45] Further evidence shows that Lactobacillus strains isolated from fecal samples possess relevant probiotic properties, including resistance to adverse gastrointestinal conditions and antimicrobial activity against pathogens such as *Staphylococcus aureus* and *Escherichia coli*.[46,47]

The scientific literature indicates differences in the presence of *Firmicutes*, which are found in large numbers in both exclusively breastfed and formula-fed infants.[49] Notably, formula-fed infants have a higher number of these bacteria, which may be related to the production of short-chain fatty acids (SCFAs) during the first four months of life. These SCFAs are produced through specific fermentation pathways, including acetyl-CoA and succinate fermentation to butyrate, and are significantly more abundant in formula-fed infants. SCFAs play an important role in regulating food intake and are associated with changes in body weight, highlighting their potential clinical relevance in early-life feeding behavior. This production may influence infants' feeding responses and possibly reduce their receptivity to food.[50] Additionally, the presence of *Firmicutes* suggests an essential role in the initial colonization of the gut, with genera such as *Streptococcus* and *Veillonella* acting as probiotics and immunomodulators, contributing to the development of the infant immune and digestive systems. These effects may be partly explained by probiotic adaptations to the intestinal environment, including changes in membrane protein and fatty acid composition, the ability to inhibit pathogen adhesion to intestinal mucus, and tolerance to bile salts, which supports microbial persistence and host-microbe interactions.[45]

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Regarding the genus *Clostridium*, studies have shown that infant formula enriched with HMOs reduces the incidence of *C. difficile* and makes the gut microbiome composition more similar to that of exclusively breastfed infants.[51] The study by Plaza-Díaz et al.[52] also suggests that *Clostridium sensu stricto* develops more strongly in infants fed the innovative formula studied. Holst et al. (2023)[53] examined HMO-supplemented infant formula and found that the relative incidence of opportunistic pathogens, including *C. difficile* and *E. coli*, was lower in the groups receiving the HMO-supplemented formula than in the control group.

The genus *Akkermansia*, detected in several of the studies examined, can degrade HMOs and promote syntrophy with beneficial bacteria, contributing to a healthy gut microbial network in formula-fed infants.[48]

Regarding mode of delivery, our results show that infants born by CS have lower microbial diversity and a higher incidence of opportunistic pathogenic species. Figure 1 illustrates this difference and highlights the lower initial diversity in CS compared to VD. The absence of passage through the maternal birth canal is a key factor in these differences.[9–12,54] Infants born by CS have a different gut microbiome composition, with a lower frequency of *Bacteroides* and *Bifidobacterium* and a higher presence of *Klebsiella*, *Veillonella*, and *Enterococcus* compared to infants born by VD.[23,24,55]

Colonization with *Klebsiella*, *Veillonella*, and *Enterococcus* is particularly common in infants delivered by CS or those who are formula fed. CS disrupts the natural microbial colonization of the newborn, promotes the growth of opportunistic bacteria, and potentially increases the risk of adverse disease.[55–57]

Given the potential negative effects of CS, formula feeding is associated with lower microbial diversity than BF in newborns delivered by CS.[30,54,58] In contrast to breast milk, infant formula may not provide the same benefits for gut colonization. Although it contains ingredients with purported benefits, these are artificial and cannot mimic the effects of their natural counterparts.[54]

Therefore, BF, especially when exclusive, plays a fundamental role in restoring the gut microbiota by promoting the growth of beneficial bacteria such as *Bifidobacterium* and *Bacteroides*.[24,41,42,55,59] This microbiota is important for protecting infants from respiratory infections and allergies.[54,55]

Conclusion

The gut microbiota is a dynamic and unique ecosystem influenced by many factors, including diet, genetics, and environment. This ecosystem plays a central role in health and development during childhood and affects the risk of disease. Variability in microbial composition leads to different results across studies, highlighting the complexity of the topic and emphasizing the importance of scientific literature in expanding knowledge about this diversity.

Choosing infant formulas enriched with prebiotics or HMOs may support the development of a healthier microbiome, more similar to that of breastfed infants, and reduce the risk of colonization by potentially harmful bacteria. Despite advances in the formulation of breast milk substitutes, it is important to emphasize exclusive BF up to six months of age and continued BF up to two years or beyond, as recommended by health authorities.

In addition, promoting VD is fundamental to reducing risks for mothers and newborns, accelerating maternal recovery, and optimizing health resources. As a public health strategy, authorities should invest in health education, training multiprofessional teams, and ensuring safe, humanized conditions to increase pregnant women's confidence and encourage the choice of this delivery method whenever possible, thus helping strengthen the baby's immune system through the development of the intestinal microbiota.

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