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MINIREVIEW

Building Robust Assemblages of Bacteria in the Human Gut in Early Life

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ABSTRACT The neonatal body provides a range of potential habitats, such as the gut, for microbes. These sites eventually harbor microbial communities (microbiotas). A "complete" (adult) gut microbiota is not acquired by the neonate immediately after birth. Rather, the exclusive, milk-based nutrition of the infant encourages the assemblage of a gut microbiota of low diversity, usually dominated by bifidobacterial species. The maternal fecal microbiota is an important source of bacterial species that colonize the gut of infants, at least in the short-term. However, development of the microbiota is influenced by the use of human milk (breast feeding), infant formula, preterm delivery of infants, caesarean delivery, antibiotic administration, family details and other environmental factors. Following the introduction of weaning (complementary) foods, the gut microbiota develops in complexity due to the availability of a diversity of plant glycans in fruits and vegetables. These glycans provide growth substrates for the bacterial families (such as members of the *Ruminococcaceae* and *Lachnospiraceae*) that, in due course, will dominate the gut microbiota of the adult. Although current data are often fragmentary and observational, it can be concluded that the nutrition that a child receives in early life is likely to impinge not only on the development of the microbiota at that time but also on the subsequent lifelong, functional relationships between the microbiota and the human host. The purpose of this review, therefore, is to discuss the importance of promoting the assemblage of functionally robust gut microbiotas at appropriate times in early life.

KEYWORDS early life, gut microbiota, infants

WHY IS THE GUT MICROBIOTA OF EARLY LIFE IMPORTANT?

In adult humans, the gut harbors a complex microbial community that is largely comprised of bacterial species and often referred to as the microbiota (1). The taxonomic composition of the microbiota is individualistic and remains relatively stable over a reasonable period of time (2, 3). Detailed knowledge of the composition of the gut microbiota, as revealed by the study of feces of westerners, is available due to the use of high-throughput DNA sequencing methods and bioinformatic analysis of data (1). In addition, metagenomic studies have revealed the constancy of metabolic capacity of the microbiota between individual humans despite differences in taxonomic content (4). Communities with high α-diversity (numerous kinds of bacteria) are considered desirable because they have functional resilience due to metabolic redundancies (5–8). Thus, loss of a species due to ecological perturbation need not result in a loss of function that might impair normal host-microbiota relationships; this represents a kind of "insurance policy." Therefore, constancy (robustness) of functional characteristics of microbiotas is desirable (9, 10).

The newborn human does not acquire the gut microbiota as a complete entity. Rather, just as the child develops physically and mentally over a timespan of years, the development of the gut microbiota also proceeds in a longitudinal, more or less predictable manner, mainly associated with changes to the dietary intake of the child (11–21). Although it might seem sensible to implant a complete microbiota from healthy

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parents in the gut of progeny immediately after birth (hereditary acquisition of microbiota lineages), the nutritional requirements of the infant do not support the establishment of an adult (climax) microbial community. The substrates required for the growth of many members of the *Lachnospiraceae* and *Ruminococcaceae*, for example, which are major taxa comprising the adult microbiota, are absent in exclusively milk-fed babies (22, 23).

Interest in the development of the gut microbiota during early life of humans has been stimulated by the desire to ameliorate childhood conditions such as the effects of preterm birth (24–26), allergies, asthma, eczema (27–30), sleep disorder (31), autistic spectrum disorder (32–35), type 1 diabetes (36), malnourishment (37, 38), and obesity (39). Further, as well as assisting in the optimal physiological development of tissues and organs, the development of a functionally resilient microbiota established by good dietary habits in childhood might contribute to better health long term due to lessening the impacts of metabolic diseases in the fifth decade of life and beyond (40–42). Thus, research of the gut microbiota in early life has three worthy goals. These goals are to understand the ecological processes that drive the establishment of bacteria in the infant gut and the impact of the neonatal microbiota on formative processes in the infant and to define the progression that culminates in a robust assemblage of species and associated functions characteristic of the adult microbiota.

THE PIONEERS

Historical studies assumed that the infant *in utero* was sterile (the sterile womb paradigm) and that first contact with bacteria occurred during passage through the birth canal. Although it makes sense that the infant develops in an environment protected from potential pathogens prior to birth, some studies have challenged this concept and have described the detection of bacterial DNA in amniotic fluid and fetal tissues (skin, lung, thymus, spleen, and gut) (43–47). It has been reasoned that an "amniotic microbiota" might impact on the development of the fetus that is bathed in, and swallows, amniotic fluid *in utero*. A "placental microbiome" has likewise been reported (48, 49). Although receiving wide publicity, the existence of amniotic/fetal and placental microbiotas has been discounted, mainly on the basis of very low biomass in samples (suggesting contamination) and inadequately controlled PCR procedures used to search for bacterial DNA in samples (45, 50–55). It is noteworthy that bacteria are known to occur in amniotic fluid samples where prelabor rupture of membranes has happened, resulting in microbial contamination (56, 57). The historical derivation of germfree mammals by hysterectomy and hand rearing under sterile conditions provides strong evidence that the mammalian foetus *in utero* is sterile (58). However, this topic is likely to stimulate much further debate.

Also debatable is the biological importance of bacterial species detected in human milk (59–66). In the more extreme view, the infant might, through suckling, be inoculated with bacteria originating in the mother's gut microbiota. These bacteria might migrate from the gut lumen, circulating to the mammary glands within blood phagocytes (67). This prospect, too, is counterintuitive to the historical concept of breast milk as a hygienic, nutritive source for baby. Through breastfeeding, the mother provides dependent, refuge-bound offspring with nutrients from maternal reserves. The selective advantage to lactating mothers, who can provide infant nutrition without having found food recently, is substantial when food supplies are uncertain (68). Nipples make possible the direct transfer of milk from the breast to the infant digestive tract. It makes sense to keep this food supply relatively free of interference by bacteria; the microbes will otherwise remove nutrients from milk, might produce metabolites toxic to the infant, produce metabolites with unpleasant taste, or be overt pathogens. Milk expressed from the breast contains bacteria, but these are mainly bacteria characteristic of cutaneous or oral habitats. Staphylococci (especially *Staphylococcus epidermidis*) and streptococci are consistently the most prevalent and abundant bacteria detected across studies (69–74). Moreover, microbial numbers in human milk are low (usually

1×10^3 to 1×10^5 CFU/ml), suggesting contamination of milk during collection or due to suckling (retrograde inoculation) rather than colonization of the lactiferous ducts and sinuses within the breast (67, 75). Milk obtained before the infant feeds ("foremilk") is dominated by bacteria characteristic of the maternal skin microbiota, whereas after feeding ("hindmilk"), bacteria characteristic of the oral microbiota of the infant are the most common (76). Thus, there is strong evidence that human milk bacteria are allochthonous species in that they originate in other habitats.

The contribution of the maternal fecal microbiota to the early seeding of the infant gut is well established (77–84). Could it be that the proximity of the opening of the birth canal to the anus is not coincidental? Defecation by mother during childbirth is very common, including at the final "push"; the baby's head emerges usually in the best fitting orientation with the face looking toward the rectum, and there is a lot of fluid ("the waters") rinsing the area, making cross-contamination possible. Meta-analysis of fecal metagenomic data from approximately 1,900 familial subjects recruited to nine studies demonstrated the predominant influence of the maternal fecal microbiota in the acquisition of bacterial strains during the first year of life (84). *Bifidobacterium*, *Bacteroides*, *Parabacteroides*, *Faecalibacterium*, *Blautia*, and *Ruminococcus* strains were particularly involved. The fecal microbiotas of adult twins tend to be more similar in composition compared to those of their siblings (4, 85–87). This supports the view that the taxa entering the gut around the time of birth may have long-term effects on gut microbiota composition because the twins are born into the same environment, whereas the birth of siblings is distanced from them in time, space, and circumstance. Genetic influences and very long-term cohabitation effects, of course, cannot be ruled out (87, 88). Further, the fecal microbiota of infants delivered by sterile caesarean section (C-section) is more likely to lack fecal bacteria such as bifidobacteria and *Bacteroides* and is more likely to contain a diverse variety of oxygen-tolerant taxa, including those usually found on the skin and in the hospital environment (82, 89–98). This observation has been considered to indicate an influence of vaginal bacteria in early colonization but really points to the importance of the anal/birth canal proximity. Microbiological studies with C-section infants are somewhat confounded because the mothers are routinely administered antibiotics prior to delivery of the child (intrapartum antibiotic prophylaxis). "Vaginal seeding" involves the deliberate exposure, immediately after delivery of C-section infants, to vaginal secretions collected from the mother on a gauze swab (99). Based on the examination of a relatively small number of babies, vaginal seeding is reported to "partially restore" the fecal microbiotas of C-section infants (99) but does not produce the dramatic difference in microbiota composition obtained by oral inoculation of C-section infants with preparations of maternal feces ("maternal fecal microbiota transplant") (100). Moreover, the influence of the vaginal microbiota on the fecal microbiota of even vaginally delivered infants is brief. Typical vaginal bacteria (*Gardnerella vaginalis*, *Atopobium vaginae*, *Lactobacillus crispatus*, and *Lactobacillus iners*) are detected (at low relative abundance) in infant feces only within the first few days after birth (84). Some clinicians have questioned the safety of vaginal seeding because they fear increased likelihood of transfer of potential pathogens from mother to child in an ill-defined system (101). The compositional differences in microbiotas detected in infants delivered vaginally or by C-section (without vaginal seeding) disappear eventually (microbiota development converges between the two groups), so catch-up in the assembly of a characteristic infant microbiota is possible (102–104). When this happens is difficult to determine accurately because few fecal sampling times prior to 3 months after birth have been included in microbiota studies. It may occur at less than 3 months or sometimes more than 12 months after birth. The importance of these early differences in microbiota composition may be relevant to development of the immune system (asthma and allergies) or metabolic disease (obesity) according to some researchers. These conclusions are based on the relative risk of the specific diseases or conditions in vaginally or C-section delivered people later in life (105, 106).

Antibiotic administration to infants is also likely to contribute to disruption of the development of the gut microbiota. Infants born preterm commonly receive antibiotic treatment as a prophylactic measure (107–113). Of interest is the work of Vatanen

TABLE 1 Examples of differences in fecal microbiotas of infants fed human milk or cow's milk formula

	Mean % (SEM)[a]	
Bacterial family	**Human milk**	**Cow's milk formula**
Bifidobacteriaceae	**61.36 (6.28)**	**40.99 (5.16)**
Lachnospiraceae	**4.22 (2.65)**	**22.11 (4.52)**
Erysipelotrichaceae	**0.21 (0.15)**	**7.99 (2.34)**
Enterobacteriaceae	8.22 (2.40)	4.42 (1.14)
Coriobacteriaceae	6.10 (2.67)	4.59 (2.20)
Streptococcaceae	**4.12 (2.81)**	**4.04 (1.46)**
Clostridiaceae	**2.67 (1.33)**	**6.23 (2.80)**
Enterococcaceae	**0.88 (0.38)**	**3.80 (0.83)**
Bacteroidaceae	**4.93 (1.99)**	**0.03 (0.02)**
Lactobacillaceae	**1.75 (0.69)**	**0.07 (0.03)**
Veillonellaceae	1.59 (0.81)	0.26 (0.12)
Peptostreptococcaceae	**0.19 (0.10)**	**0.94 (0.56)**
Ruminococcaceae	0.35 (0.24)	0.64 (0.42)

[a]Relative abundances of the 13 most highly represented bacterial families in the feces of 2-month-old infants fed human milk or formula; 30 infants per group (data from reference 120) are presented. Statistically significantly different values are indicated in boldface.

et al., who found a differential effect of antibiotic treatment on bifidobacterial species: *B. longum* and *B. breve* populations appeared to be relatively unscathed by antibiotic exposure compared to the other common bifidobacterial species detected in the gut microbiota of infants (109). Also of note, the size of bifidobacterial populations in the fecal microbiota is inversely related to the prevalence of antibiotic resistance determinants detected in the microbial community (108).

ASSEMBLY OF THE MICROBIOTA INVOLVES AN ECOLOGICAL SUCCESSION

Regardless of source of inoculating bacteria and other potential confounders, the establishment of a microbiota in the infant gut in the days, weeks, and months following birth is characteristically an ecological (biological) succession. An initial, heterogeneous collection of species is replaced by specific bacterial populations, consistently detected in the majority of infants, which expand or decrease in size over time in a characteristic manner (114). The metabolic activities of the early arrivals lower the oxidation-reduction potential (E_h of meconium, +175 mV; 2-day-old infants, −113 mV) of the digesta and so provide a more suitable environment for the establishment of obligate anaerobes that will eventually dominate the microbiota. The qualitative and quantitative changes characteristic of the ecological succession are regulated by factors described as autogenic (formed within the habitat, such as competition for nutrients and E_h) or allogeneic (influences from outside the habitat, such as growth substrates in the food that is consumed) (114).

Tissier reported, in 1905, the predominance and persistence of Gram-positive bacterial cells in the feces of infants fed human milk exclusively (115). A greater variety of bacterial morphotypes was present in the feces of infants fed cow's milk. This difference between fecal microbiotas of infants fed human milk or formula (based on ruminant milk) still exists today even though modern formula resembles human milk more closely in nutritional aspects (89, 116–122). In most comparisons, members of the genus *Bifidobacterium* are abundant in the feces of infants fed exclusively human milk (relatively about 60% of the microbiota on average, but 100% of the microbiota in some infants) whereas the community has a more varied taxonomic composition when infants are exclusively formula-fed (about 40% bifidobacteria) (78, 118, 120, 123–130) (Table 1). Curiously, although fed human milk, some infants have very low relative abundances of bifidobacteria in the feces. Sometimes, none at all are detected even when more than one fecal sample is collected and examined. It is possible that these results are due to lack of sufficient sensitivity of detection methods (including poor choice of PCR primers and DNA extraction methods), in conjunction with fluctuating population levels of bifidobacteria (131, 132). However, there really may be infants who missed exposure to bifidobacteria at a critical time (the

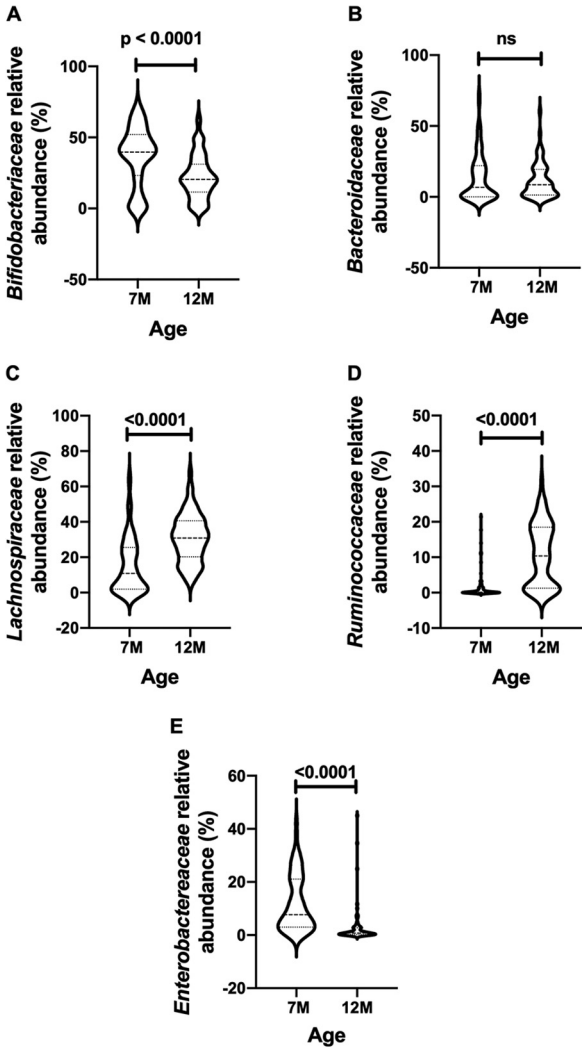

FIG 1 Examples of differences in the relative abundances of selected bacterial families detected in the feces of the same New Zealand infants (n = 74) sampled at 7 compared to 12 months of age. (A) *Bifidobacteriaceae*; (B) *Bacteroidaceae*; (C) *Lachnospiraceae*; (D) *Ruminococcaceae*; (E) *Enterobacteriaceae*. The data are from reference 20.

"window of opportunity/infectivity"). Normally, however, bifidobacteria predominate in the microbiota of infants during the exclusively milk fed period of life.

The relative abundance of bifidobacteria begins to decline once weaning (the introduction of solid foods to the diet, complementary feeding) begins, usually at 4 to 6 months of age in western countries. The intake of milk (both human and formula) declines from then on and, concomitantly, an increased amount of plant glycans (dietary fiber) is consumed (20). Thus, growth substrates for bacteria provided by milk are reduced in concentration in the gut, while those associated with "solid" foods increase. The increasing complexity of the diet between 6 and 12 months of age provides a wider range of potential growth substrates for obligately anaerobic bacteria that have degradative and fermentative capacities in relation to dietary fiber (11, 14, 17, 18, 133–135). Therefore, the diversity of bacterial types comprising the microbiota increases because, although population sizes of *Bifidobacteriaceae* are reduced and *Bacteroidaceae* remain much the same, those of *Lachnospiraceae* and *Ruminococcaceae* are increased. The relatively large *Enterobacteriaceae* population of early life declines in size as the obligately anaerobic taxa that produce short-chain fatty acids, inhibitory to the enterobacteria, establish and proliferate in the gut (15, 20, 136, 137) (Fig. 1). Stewart et al. (138) provided a comprehensive view of the development of the fecal

microbiota of approximately 900 children, at risk of developing type 1 diabetes, which were recruited in various locations in the United States and Europe and sampled monthly from 3 months of age. Three phases of microbiota development could be recognized using 16S rRNA gene and metagenomic sequence analysis: a "developmental" phase (months 3 to 14), a "transitional" phase (months 15 to 30), and a "stable" phase (months 31 to 46). Particular taxa were identified as markers of each phase because of changes in relative abundances over time (for example, bifidobacteria in the developmental phase, *Subdoligranulum* and *Anaerostipes* in the transitional phase, and the *Eubacterium rectale* group in the stable phase). Based on taxonomic criteria, most studies point to the assembly of an adult-type microbiota by 2 years of age, but further research may show that the process continues for an extended time (139–144). Firm conclusions will not be drawn until gaps in the sampling of age groups 3 to 6 years, 6 to 12 years, and 12 to 18 years have been filled (141). Nevertheless, biochemical features of adult feces that reflect bacterial degradation of human secretions (decreased protease activity, increased mucin and bilirubin degradation, and cholesterol reduction to coprostanol) generally appear by age 12 to 24 months (145–150).

Although a general pattern, outlined above, of assembly of the gut microbiota of infants can be recognized, confounding factors modify the acquisition of the microbiota. For example, ethnic differences in microbiota composition can be detected even prior to the start of complementary feeding in Chinese, Malay, and Indian infants living in Singapore (103). Ethnic differences in microbiota composition point to the potential impact of human genetics, and/or fecal microbiotas of family members, and/or general household environment on the development of the gut microbiota (142, 151, 152). All things considered, the genotype of the host probably has little impact on the composition of the adult microbiota, but the situation in infants has not been investigated comprehensively (153–156). Differences in gut microbiota compositions between ethnic groups prior to weaning might also be due to environmental factors such as dietary preferences of the mother and other household members that could select for particular bacterial strains that would be dispersed to the infants (142, 157, 158). Humans sharing the same environment tend to have microbiotas that are more similar in composition, indicating greater dispersal/acquisition of gut bacteria (159–162).

Environmental ecologists support the "Baas Becking hypothesis" in which it is postulated that all types of microbes occur in all soils, no matter where ("everything is everywhere"), but that the properties of different soils in different locations favor the assemblage of microbial communities of different compositional proportions ("but the environment selects") (163). Equally, the infant gut may be exposed to bacterial species from a variety of sources, but a characteristic community, of different complexity to that of the mother's adult microbiota is assembled during the first 3 months of life. This infant community is simple in composition (low alpha-diversity), dominated by the family *Bifidobacteriaceae*, in contrast to the highly diverse microbiota of an adult. The differences in complexity provide something of a conundrum because, ecologically, high diversity equates to functional resilience. Perhaps the functional requirements of the microbiota of infants are quite simple at this stage of life and so can be provided by a simple but highly networked community? The relatively limited nutritional resources available to bacteria in the habitat could be depleted by a low diversity, yet metabolically highly specialized, community that would ensure competitive exclusion of pathogens. In contrast, in a more complex nutritional environment, a higher diversity microbiota would be required to fill all of the ecological niches (164). With these differences in view, the bowel of exclusively human milk-fed infants is likely to provide an example of environmental selection due to the provision of a "fertile soil" in which a limited collection of specialized bacteria can thrive (165).

HUMAN MILK OLIGOSACCHARIDES PROVIDE A "FERTILE SOIL" FOR SOME BACTERIAL SPECIES

Complex carbohydrates, synthesized in the mammary glands, form the third most abundant solid component of mature human milk (10 to 15 g/liter) (166–168). They are

referred to as human milk oligosaccharides (HMOs), of which there are at least 150 types (169, 170). These are constructed from five building blocks: glucose, galactose, *N*-acetylglucosamine, fucose, and sialic acid. In general, they consist of a lactose core linked to lacto-*N*-biose or to *N*-acetyllactosamine. The lactose core can be elongated at the C-3 position of galactose with repeats of lacto-*N*-biose (Galβ1-3GlcNAc; referred to as type 1 chain) or *N*-acetyllactosamine (Galβ1-4GlcNAc; type 2 chain) (171). The terminal lactose in the chains may be linked to fucose (α1-2, α1-3, or α1-4 linkages) or sialic acid (*N*-acetylneuraminic acid [Neu5Ac]; α2-3 or α2-6 linkages) (172, 173). Fucosylation depends in part on the "secretor" status of the mother; the *FUT2* gene encodes a fucosyltransferase and results in milk containing α1-2 fucosylated HMOs. These are absent in the milk of "nonsecretor" mothers because they have a *FUT2* gene that encodes an inactive protein (174, 175). Elongation of chains can occur at the C-6 position of galactose, resulting in branched molecules. HMOs can be separated from human milk to give an acidic fraction (mostly sialylated oligosaccharides; 12 to 14% of HMOs in milk) and a neutral fraction containing oligosaccharides that may be fucosylated (35 to 50% of HMOs in milk) or nonfucosylated (42 to 55% of HMOs in milk) (176). HMOs that have a type 1 chain linkage (such as lacto-*N*-tetraose [LNT]) are not degraded by human β-galactosidase in the small bowel, whereas those with a type 2 linkage (such as lacto-*N*-neotetraose [LNnT]) are susceptible to cleavage (171). However, type 1 chains are predominant in human milk, and it is considered that much of the HMO fraction of milk is not digested in the small bowel but passes to the colon where the oligosaccharides are metabolized by bifidobacterial species (172). *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides fragilis*, and *Akkermansia muciniphila* are also able to degrade HMOs because HMO structures make them similar to those of mucin oligosaccharides (Lewis antigens) (177, 178). The *Bacteroides* species are more abundant in the feces of infants fed human milk than cow's milk formula, indicating that HMOs enrich for these bacteria, too, and divert their degradative activities away from mucins in the mucus layer lining the gut (120, 179, 180). The molecular mixture of HMOs detected in human milk varies between mothers but remains constant, per individual, throughout lactation. However, quantities diminish with time (168, 181–187). Comparison of the amounts and structures of HMOs in human milk of mothers and the feces of their infants provides evidence of transit of HMOs through the gut and degradation of at least some of these structures by bacteria, as well as bacterial utilization of carbohydrates linked to proteins (*N*-glycans) (185–187).

The common bifidobacteria detected in global studies of infant feces fed human milk include *B. longum* subspecies *infantis*, *B. longum* subsp. *longum*, *B. breve*, and *B. bifidum*. Other species detected in some studies include *Bifidobacterium animalis* subsp. *lactis*, *Bifidobacterium pseudocatenulatum*, *Bifidobacterium dentium*, *Bifidobacterium adolescentis*, *Bifidobacterium catenulatum*, *Bifidobacterium kashiwanohense*, and *Bifidobacterium scardovii* (78, 120, 123, 126, 188–192). There is a good biochemical fit between the common bifidobacterial species and HMOs because the bifidobacteria produce fucosidases, hexosaminidase, sialidase, biosidase, and galactosidases that hydrolyze the oligosaccharides (170, 193–212). These enzymes are located at the cell surface of *B. bifidum*, whereas they are intracellular in *B. longum* subsp. *infantis* and subsp. *longum* and in *B. breve* (213). Thus, HMOs are internalized by the latter species before hydrolysis occurs, whereas cleavage of the oligosaccharides by *B. bifidum* results in accumulation of fucose and sialic acid in the extracellular environment because the bacteria do not use these substances for growth (205, 214–216). Fucose and sialic acid are, however, growth substrates for some strains of *B. breve*, thus providing an opportunity for syntrophy between the two species (214, 215). However, cleavage of fucose or sialic acid from simple HMOs such as 2′-*O*-fucosyllactose (2FL) or 6′-*O*-sialyllactose also liberates lactose that is utilized for growth by both *B. bifidum* and *B. breve*. Therefore, a seemingly beneficial cross-feeding interaction between the bifidobacterial species might become competitive (215). *In vitro*, *B. bifidum* has been shown to adjust to the situation because its abundance is the same in monoculture as in coculture with *B. breve* in medium containing 2FL. *B. bifidum* achieves this in coculture by

increasing transcription of the fucosidase gene so that more lactose becomes available and by increasing transcription of genes associated with carbohydrate transport and with energy production and conversion (215). *B. bifidum* also has the capacity to use mucin as a substrate, perhaps explaining why it persists in the feces of infants even when weaned, at which time HMOs are no longer available (217–219). The biochemical pathways associated with the utilization of HMOs by bifidobacterial species has been well reviewed recently by Sakanaka et al. (211). There is more lactose in human milk than the infant can utilize (traces can be detected in infant feces), so this substance, too, is available for microbial growth (132). Much more information about the intricacies of metabolic interaction among bifidobacteria is required in order to understand nutritional regulation of these populations.

Efficiency of use of HMOs and their component parts for growth is markedly different between bifidobacterial species and can be used to differentiate between them in laboratory culture (Fig. 2). *B. longum* subsp. *infantis* has much the best growth on HMO substrates, probably because of the expression of a cluster of genes that form an HMO utilization locus in the genome of the bacteria (206). The capacity of subsp. *infantis* to preferentially utilize and efficiently grow on the most abundant (especially fucosylated) HMOs (220, 221) should ensure its dominance in the gut of infants fed human milk, yet this seems not always to be the case. Infants in California and in some other regions of the United States, as well as in particular countries, are reported to have low abundances of subsp. *infantis*. However, data are relatively sparse, and it is difficult to gain a good global perspective (95, 124, 130, 189, 192, 222–227). A paucity of subsp. *infantis* could be related to feeding practices, or perhaps some environments are not conducive to the transmission of subsp. *infantis* (224). Nevertheless, bifidobacteria in general are abundant in the gut microbiota of infants, and bacterial genes associated with HMO utilization are more abundant in fecal DNA when infants are receiving human milk than during weaning (109).

BIFIDOBACTERIAL FUNCTIONS IN RELATION TO INFANT WELL-BEING

A preponderance of bifidobacteria in the gut may mediate competitive exclusion of bacterial pathogens by virtue of the creation of an acidic environment due to fermentation products acetate and lactate (propanediol in the case of fermentation of fucose by *B. longum* subsp. *infantis* and *B. breve*) (215, 228). Fecal pH of infants fed human milk is lower than that of formula-fed (cow's milk-based) infants (229–232). Although the amount of historical data are limited, some investigators argue that fecal pH of western infants may have increased temporally due to a paucity of subsp. *infantis* in the gut microbiota (233). Infants fed formula have a fecal metabolome suggestive of greater metabolism of peptides and amino acids than do human milk-fed infants. This probably reflects the lower oligosaccharide content of formula, higher protein content of formula, different microbiota composition, and slower gut transit time in formula-fed infants compared to those fed human milk (234, 235).

Apart from a competitive exclusion role, bifidobacteria may be important to infant development because they produce folate (vitamin B_9), which is a coenzyme or cosubstrate in single-carbon transfers in the synthesis of nucleic acids and metabolism of amino acids (13, 236). An important folate-dependent reaction is the conversion of homocysteine to methionine in the synthesis of *S*-adenosylmethionine, a methyl donor. Another folate-dependent reaction, the methylation of deoxyuridylate to thymidylate in the formation of DNA, is required for proper cell division (237). The enrichment of genes involved with the *de novo* biosynthesis of folate (known to be absorbed from the colon) in infants relative to the favored synthesis of another B vitamin, cobalamin, in adults is interesting because it provides circumstantial evidence that folate production in the infant gut is of developmental significance (13, 238).

A baby's brain is only 15% formed at birth and in 3 years increases in weight from 300 g to 1.2 kg and exceeds the rate of growth of any other organ or body tissue (239). The infant is born with neurons already formed but the synaptic connections between these cells are mostly established and elaborated after birth, causing a large nutritional

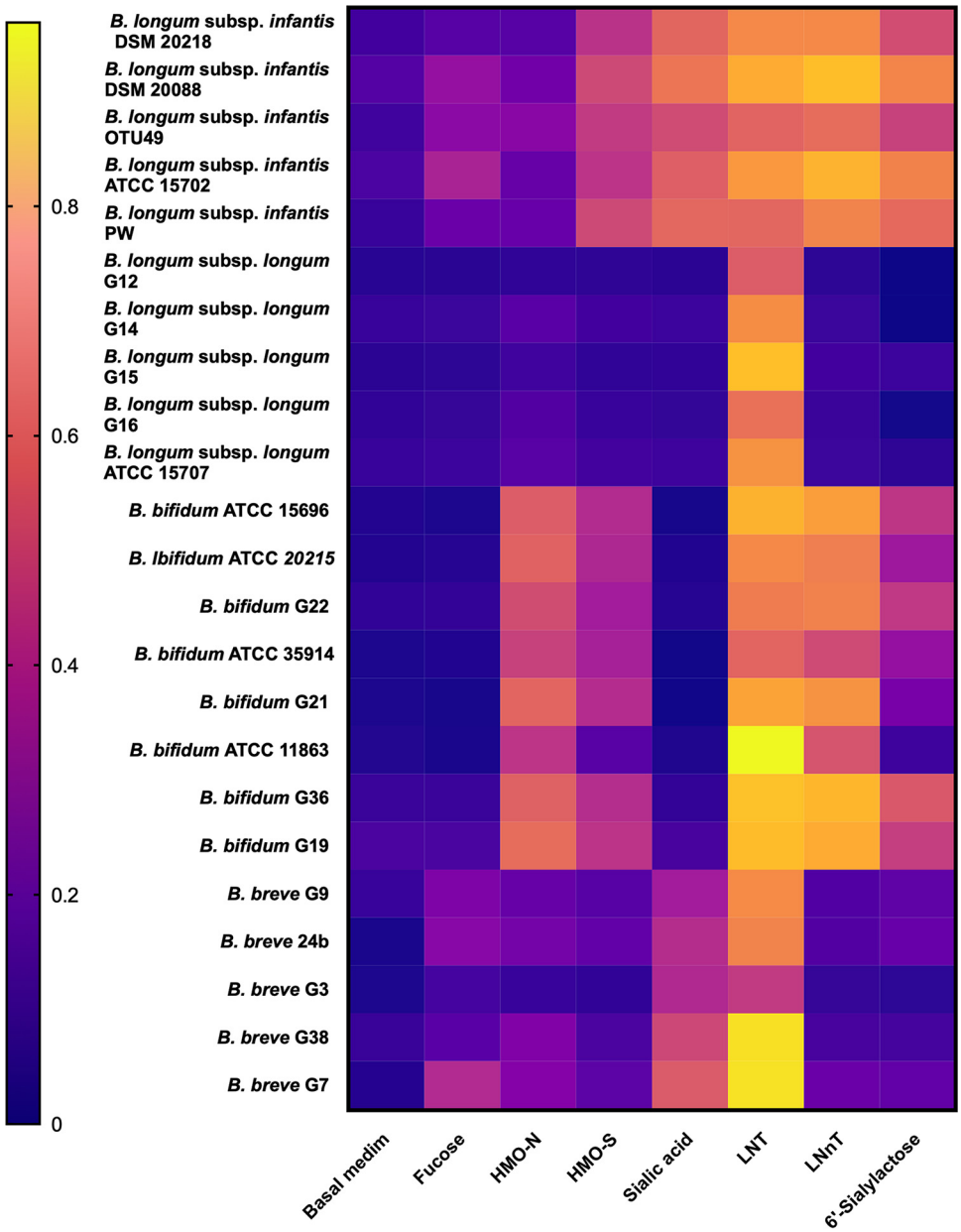

FIG 2 Heat map showing the growth (optical density after 24 h anaerobic incubation) of bifidobacterial species (*B. longum* subsp. *infantis*, *B. longum* subsp. *longum*, *B. bifidum*, and *B. breve*) in media containing HMO fractions (0.2% [wt/vol]) or component molecules (0.2% [wt/vol]) or basal medium (no added carbohydrates). The data are from references 191 and 215.

demand for the biosynthesis of gangliosides. Nutrition of the infant in early life affects developmental processes, including cognition (240–243). While long-chain fatty acids in milk (such as docosahexanoic acid) have been the focus of much of this research, there is tantalizing evidence that sialic acid is also important for optimal brain development and cognition (244, 245). Sialylated oligosaccharides are detectable in the blood of infants and the sialic acid content is higher in the brain of human milk-fed infants relative to formula-fed infants (246–248). Perhaps metabolism of HMOs by bifidobacterial species, particularly the extracellular sialidase activity of *B. bifidum*, makes a contribution to this phenomenon?

Many clues to the influences of the gut microbiota on the mammalian host have been obtained from comparisons of the biochemical and physiological characteristics

of germfree mice with conventional animals (which have a microbiota) (249). Among the differences in these animal groups is the underdevelopment of immune features, including the lesser size of ileocecal lymph nodes and the gamma-globulin fraction of blood of germfree animals. Experiments with ex-germfree mice colonized by a gut microbiota show that the presence of the bacteria programs the immune system toward tolerance of members of the microbiota while still retaining the ability to prevent invasion and dispersion of pathogens in the body (29, 250–255). The maintenance of this homeostasis is dependent on tightly controlled immune responses as well as partitioning of functions (mucosal relative to systemic immunity) (256–258). Modulation of immune function can be achieved for the most part by inoculating adult ex-germfree mice at any age with a gut microbiota (259). However, the ability to restore some cellular defects (for example, negating the mucosal accumulation of invariant natural killer T cells in gut mucosa) that occur in the absence of the microbiota is restricted to a short time interval in early life and thus is age dependent (29, 259). Therefore, the members of the gut microbiota in very early life of humans may have important interactions with the developing immune system. In this context, a variety of molecules associated with bifidobacterial cells are reported to stimulate aspects of the immune system, and the size of bifidobacterial populations has been correlated with the amount of salivary sIgA production and B cell maturation (260–263). Bifidobacterial effects on the expression of the dendritic-cell activation marker CD83 and the production of interleukin-10 (IL-10), as well as response to vaccinations by human infants, have been reported (124, 192). Infants inoculated with the EVC001 strain of *B. longum* subsp. *infantis* harbor abundant bifidobacteria in the gut, and there is a negative correlation with fecal cytokines IL-13, IL-17A, IL-21, and IL-33 that indicates a silencing of Th2 and Th17 responses in the gut. This phenomenon may be mediated by a specific metabolite (indole-3-lactic acid) produced by bifidobacteria when they utilize HMOs (264). However, overall, research on this topic seems to lack cohesion and relation to real life. It may indeed be an intractable situation given that few babies have low or absent bifidobacterial populations for comparative purposes, that low bifidobacterial populations are counterbalanced by those of other bacterial species, and that sampling of appropriate immune features is difficult and therefore very limited in neonatal humans.

The maternal production of milk rich in substances that do not obviously contribute to the nutrition of the child is certainly curious and indicates a phenomenon of evolutionary importance. As well as providing "fertilizer" to encourage a predominance of bifidobacteria in the colon that could contribute to competitive exclusion of pathogens in the gut and assist infant nutrition as indicated above, HMOs probably also contribute to host defense through decoy functions in that they resemble receptors in the gut mucosa to which pathogens, including viruses, may bind. "Mopping up" pathogens in the gut lumen with HMOs would minimize opportunity for mucosal adherence and infection to occur. Examples of possible decoy roles apply to the bacterial pathogens *Campylobacter jejuni*, enteropathogenic *Escherichia coli*, viruses such as norovirus, and the protozoan *Entamoeba histolytica* (265–270). However, some caution is required because G10P[11] rotavirus infection of neonates has been reported to be facilitated by the presence of HMOs (271). *In vitro* studies indicate inhibitory effects of HMOs on some bacteria and promotion of epithelial cell integrity (272–277). These effects may be specific to particular HMOs (268).

THE RESEARCH PATH AHEAD

Human milk for human infants in the months following birth is clearly the desired option to satisfy the nutritional requirements of the child. Exclusive breast milk feeding during the first 6 months of life and partially breast milk-feeding during weaning, is recommended by the World Health Organization, as well as by professional medical associations and agencies (278). Maternal antibodies in milk, iron-sequestering molecules, and molecular decoys help provide protection of the newborn infant from

infections (279, 280). For example, data gathered from about 20,000 mother/infant pairs at a time when antibiotics were not available in pediatrics (1930s), show that infants fed totally "artificially" demonstrated 3-fold-higher morbidity and 7-fold-higher mortality from gastrointestinal disease than infants fed human milk. Partially artificially fed infants had 2.5 times more morbidity and 3 times higher mortality than infants fed human milk (279, 281). HMOs are probably molecular decoys allied to protection from infection but collaterally encourage the development of an abundant bifidobacterial population in the gut microbiota during the period of exclusive human milk feeding. The bifidobacterial population commonly contains several species that have varying abilities with respect to utilization of HMOs. The relative efficiency of utilization of HMOs by different bifidobacterial species has been studied, but the interactive relationships between species and between bifidobacterial and other gut inhabitants has only been studied superficially. There is a need, therefore, to define how a stable (robust) microbiota is maintained during the first months of life, probably by means of cooccurrence or metabolic networks (282, 283). Once identified, the trophic networks could be established using *in vitro* systems, probably including simple chemostats (215) and tested for resilience when nutritional factors are altered.

The early contribution of bacterial strains from maternal feces to infants is likely to be very important, but further research is needed to establish specific effects resulting from this early seeding. Indeed, murine studies using antibiotic-treated and gnotobiotic animals suggest that, even before birth, the maternal gut microbiota influences the concentrations of numerous molecules in maternal serum and hence in fetal brain (284). Thus, the maternal microbiota metabolism may influence neural development even *in utero*! An exciting prospect is therefore the study of the influence of maternal microbiota pre- and postpartum to delineate a potentially critical and long-term relationship that goes beyond the usual mother-child nurture.

Modification of infant formula will continue to be made so as to increase the oligosaccharide content and provide "probiotic" bacteria that might function in the gut ecosystem. Space limitation does not allow substantial review of these two topics, but examples are provided with comments in Table 2. The nascent use of synthetic HMOs, 2′-*O*-fucosyllactose (2FL) and lacto-*N*-neotetraose (LNnT) as additives for infant formula is of considerable interest (325–328). 2FL is the major HMO in milk from secretor mothers, comprising almost 30% of all HMOs present (327). As discussed above, the enrichment of bifidobacteria in the infant gut may not be the sole evolutionary function of HMOs and galacto- and fructo-oligosaccharides (GOS/FOS) are only able to provide growth substrates for bacteria. Thus, the inclusion of synthetic HMOs in formula may be an important advance. To date, trials with infants indicate that formula supplemented with 2FL/LNnT is safe for ingestion by neonates (329, 330), but the bifidobacterium-stimulating effect is likely to be species-specific because some bifidobacteria (for example, strains of *B. breve*) cannot metabolize these HMOs (Fig. 2) (191, 215). The few microbiological investigations of infants fed supplemented (synthetic HMOs) relative to nonsupplemented formula are somewhat unsatisfactory because the bifidobacterial data are superficial and the numbers of infants examined are small (328). The use of LNnT in formula is curious because it is susceptible to cleavage by human β-galactosidase (171). Caution about reliance on the addition of single HMOs is suggested because different developmental effects of human milk in the infant might relate to specific HMOs. Certainly, the addition of one or two HMOs to formula does not replicate the features of human milk where a diversity of HMO structures is a characteristic feature.

In-depth knowledge of the immunological influences of bifidobacterial species in very early life requires more research. Specifically, we need to know whether they are the critical bacterial species that affect the aspects of immune development that, as mentioned above, cannot be replicated in older gnotobiotic animals. Since most human infants are naturally exposed to bifidobacteria, much of this work will probably require comparisons of germfree and gnotobiotic animals exposed to bifidobacteria

TABLE 2 Examples of probiotic, prebiotic, and synbiotic approaches to influencing the assemblage of gut microbiota in infants

Approach	Organism	Description
Probiotics	*L. rhamnosus*	In separate studies, *Lactobacillus rhamnosus* strain GG or strain HN001 (DR20) was administered to mothers whose children were at high risk of developing allergies. The probiotic was taken by mothers before the baby was born and was administered postnatally to the infants for 6 months. The occurrence of atopic eczema at 2 years of age was recorded as the main point of comparison between placebo and test groups. Atopic eczema was diagnosed in 50% fewer probiotic-administered infants compared to controls (285, 286). Strain HN001 was shown to be present in about 60 to 70% of the infants in the test group (5% in the placebo group) when feces were tested on a single occasion during the course of the study (286). Thus, efficacy could be linked to the passage of the probiotic strain through the gut. Probiotic trials like this do not relate directly to the natural situation where lactobacilli, although detectable, are present at low relative abundances in the gut microbiota compared to values associated with the common bifidobacterial species (120). Nevertheless, there has been much pediatric interest in this topic, and there is an extensive review literature regarding the impact of the administration of probiotic products on the prevalence of allergies and atopy in children (287–293). In general, clinical views of the effectiveness of these products are rather mixed.
	B. infantis (presumbaly *B. infantis* subsp. *infantis; B. bifidum* included in later versions of this product) and *Lactobacillus acidophilus* or *B. breve* M-16V	Premature, very-low-birthweight infants (<1,500 g) are highly susceptible to necrotizing enterocolitis (NEC) wherein the infants show poor feeding and spilling of gastric contents (which may be bile stained), abdominal distension, and blood in feces. Necrotic inflammation of the intestine may lead to perforation and bacterial infection and, potentially, NEC has high mortality (294). Reduction in historical rates of NEC have been reported when administration of these probiotics to infants in neonatal intensive care has been introduced as a routine practice (295–300).
	B. animalis subsp. *lactis* BB-12	Administration of formula containing *B. animalis* subsp. *lactis* BB-12 augments bifidobacterial abundance in the feces of preterm infants, and enterobacterial proportions are reduced (302, 303).
Synbiotic	*B. breve* M-16V, galacto- and fructo-oligosaccharides	Feeding formula containing *B. breve* M-16V in combination with short-chain galacto-oligosaccharide and long-chain fructo-oligosaccharide augments bifidobacterial proportions in the microbiota of C-section infants. Both the probiotic strain and naturally colonizing *B. breve* strains were boosted in the infant gut. Fecal pH was lowered compared to controls due to increased acetate production by the microbiota, and there was a reduction in the proportion of *Enterobacteriaceae* (301).
Prebiotics	Galacto- and fructo-oligosaccharides	Efforts have been made to increase the oligosaccharide content of formula by the addition of naturally occurring or synthetic oligosaccharides. Galacto- and fructo-oligosaccharides (GOS and FOS, respectively) are common prebiotics used for this purpose (304–308). Commercially available GOS contain oligosaccharides composed of galactose residues that are variously linked β-D-1,2, β-D-1,3, β-D-1,4, and β-D-1,6 and range in degrees of polymerization (DP) from 2 to 5. Each oligosaccharide is terminated with a glucose residue. FOS contain two series of β-D-2,1-linked fructo-oligosaccharides, one of which contains a terminal glucose (GF series, with DPs of 2 to 6) and one which does not (F series, with DPs of 2 to 6) (309–311). As such, GOS and FOS do not chemically resemble HMOs, but various bifidobacterial species are known to utilize GOS and FOS for growth in laboratory experiments (312–314). Inclusion of the substrates in formula tends to result in somewhat augmented total bifidobacterial populations in infant feces relative to controls (315–322). In coculture experiments, *B. breve* has demonstrated the greatest trophic potential with respect to GOS/FOS to outcompete the subspecies of *B. longum* (323). Unfortunately, the *in vivo* effect of GOS/FOS dietary supplementation on the proportions of the different species within bifidobacterial populations has not been included in trials in which the outcome of feeding supplemented formula has been compared to that of nonsupplemented formula. This may be due to past difficulties in differentiating between bifidobacterial species using DNA-based methodologies (224, 324).

and fed human milk. However, comparisons of the effects of infant formulas with or without bifidobacterial components may also be useful in this research. The success of this approach will depend on which bifidobacterial species are included in the formula and must also take into consideration the biochemical differences that exist between human milk and formulas. In other words, the background nutritional environment

may confound extrapolation of results from formula-fed infants to those fed human milk.

Although the bifidobacteria have been a major focus of the gut microbiota in early life throughout microbiological history, the predominance of these bacteria in the gut is a transient phenomenon and is largely over by just a few months postpartum. The commencement of weaning and the development of a highly diverse microbiota that provides a platform for the rest of life is equally important. Knowledge of how microbial communities with high functional resilience are constructed is required, with a particular need to understand how complex microbiotas promote health through involvement in molecular signaling in human physiology (331–334). It is relevant to this topic that there is a reduced prevalence of allergies in children whose microbiota is characterized by the end of the first year of life by an enrichment of propionate- and butyrate-producing bacteria (335, 336). The main drivers of the development of the gut microbiota after weaning and throughout the rest of life are the complex plant glycans contained in the diet (135). Therefore, encouraging the development of a functionally resilient microbiota in the first year or two of life requires that the infant be exposed to a wide spectrum of tastes and textures of the diverse foods provided by Earth's bounty. An intake of a variety of whole foods, especially those containing complex plant polysaccharides, will promote microbiotas of high functional resilience (135). Traditionally, parents have been encouraged to start spoon-feeding their infant puréed foods from around 6 months of age, progressing to mashed and then chopped foods in the hope that they will be eating family foods by about 12 months of age. An alternative method of complementary feeding, known as baby-led weaning, encourages babies to feed themselves whole pieces of food from the family meal from 6 months of age, instead of being offered "baby food" (337–341). As a result, infants following this procedure are more likely to eat the same foods as the rest of the family than their baby-food counterparts. Because the introduction of "solid" foods is a major determinant of the development of the gut microbiota, it is possible that the more rapid transition to the family diet observed in baby-led approaches could beneficially influence the assembly of the gut microbiota in these children. However, recent microbiota research in baby-led weaning, using mediation analysis, indicates that adequate intakes of "fruit and vegetables" and "dietary fiber" are critical for development of a diverse microbiota and that this may not be sustained by family foods if they are not soundly based on good nutrition for the whole family (20). Care must also be taken that the infants do not bite off more than they can chew; choking is not a desirable outcome (342).

Despite the large volume of research that has been directed to studying the bacterial taxa comprising gut microbiotas in early life, there is yet little detail about the molecular biology of microbe-human interactions. It seems quite likely that future breakthroughs in understanding the early life relationships between the gut microbiota and humans will arise from genetical (including gene transcription), biochemical, neurological, and physiological (including immunology) studies rather than predominantly taxonomic, compositional investigations. However, since much of this work will probably have to be accomplished using murine models, clear translations to human biology may be difficult to perceive given the different nutritional, gut microbiota, and developmental trajectories that occur between humans and mice. It is a difficult task worth pursuing because the early life events associated with the assemblage of the gut microbiota may impact the human host throughout its remaining life span!

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