

# The Gut Microbiota: A Promising Target in the Relation between Complementary Feeding and Child Undernutrition

Rana F Chehab, Tzu-Wen L Cross, and Michele R Forman

Department of Nutrition Science, Purdue University, West Lafayette, IN, USA

## ABSTRACT

Child undernutrition is a major public health challenge that is persistent and disproportionately prevalent in low- and middle-income countries. Undernourished children face adverse health, economic, and social consequences that can be intergenerational. The first 1000 days of life, from conception until the child's second birthday, constitute the period of greatest vulnerability to undernutrition. The transition process from milk-based diets to solid, semi-solid, and soft food and liquids other than milk, referred to as complementary feeding (CF), occurs between the age of 6 mo and 2 y. CF practices that do not meet the WHO's guiding principles and are lacking in both quality and quantity increase susceptibility to undernutrition, restrict growth, and jeopardize child development and survival. The gut microbiota develops toward an adult-like configuration within the first 2–3 y of life. Recent studies suggest that significant changes in the gut microbial composition and functional capacity occur during the CF period, but these studies were conducted in high-income countries. Research in low- and middle-income countries, on the other hand, has implicated a disrupted gut microbiota in child undernutrition, and animal experiments reveal the potential for a causal relation. Given the growing body of evidence for a plausible role of the gut microbiota in the link between CF and undernutrition, microbiota-targeted complementary food may be a promising treatment modality for undernutrition management. The aims of this paper are to review the evidence for the relation between CF and undernutrition and to highlight the potential of the gut microbiota to be a promising target in this relation. Our summary of the current state of the knowledge in this area provides a foundation for future research and helps inform the design of interventions targeting the gut microbiota to combat child undernutrition and promote healthy growth. *Adv Nutr* 2021;12:969–979.

**Keywords:** malnutrition, child growth, first 1000 days, infant and young child feeding, solid food, gut microbiome, low- and middle-income countries

## Introduction

Undernutrition refers to insufficient or imbalanced intake of energy and nutrients necessary to maintain growth and good health (1). Child undernutrition manifests in 3 forms—stunting, wasting, and underweight (1)—which are defined using weight and height (length) measurements in the index child compared with age- and sex-specific child growth standards by the WHO (2). Despite efforts to eradicate undernutrition, it remains the most common “disease”

among children under the age of 5 (3). According to recent 2020 estimates, 144 million (21.3%) children younger than 5 y are stunted and 47 million (6.9%) are wasted (4). Child undernutrition is disproportionately prevalent in low- and middle-income countries (LMICs) with South Asia and sub-Saharan Africa bearing the greatest disease burden (4).

Nearly half of all deaths in children under the age of 5 are attributable to undernutrition (5). Undernourished children are at a higher risk of death from common child illnesses such as diarrhea, pneumonia, and malaria (6), which together topped the list of the leading causes of death among children under 5 in 2015 (7). In the long term, undernutrition is linked to poorer overall health, impairments in intellectual performance, and reduced economic productivity (8). Further, a woman who was undernourished in childhood has higher odds of delivering a malnourished low-birth-weight newborn, rendering undernutrition an intergenerational

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Address correspondence to RFC (e-mail: [rchehab@purdue.edu](mailto:rchehab@purdue.edu)).

Abbreviations used: CF, complementary feeding; DHS, Demographic and Health Survey; EED, environmental enteric dysfunction; HIC, high-income country; IYCF, infant and young child feeding; LMIC, low- and middle-income country; MAM, moderate acute malnutrition; MAZ, microbiota-for-age z score; MDCF, microbiota-directed complementary food; RF, random forest; rRNA, ribosomal RNA; RUSF, ready-to-use supplementary food; RUTF, ready-to-use therapeutic food; SAM, severe acute malnutrition; SF, solid food.

problem (3). Interventions to combat undernutrition and promote healthy growth and development among children in LMICs are essential to meet the Sustainable Development Goals, namely those related to hunger eradication and reduction of inequalities (9).

Undernutrition is associated with a web of risk factors, with inadequate dietary intake and infectious diseases being proximal factors in LMICs (10). Approximately 100,000 deaths due to undernutrition in children under 5 could be prevented each year if infant and young child feeding (IYCF) was adequate (11). Environmental enteric dysfunction (EED) due to exposure to enteropathogens is another common risk factor in LMICs with poor sanitation and unhygienic conditions (12). Diarrhea, a particularly visible clinical manifestation of EED, is the second leading cause of death among children under 5, contributing to nearly 9% of deaths in 2015 (7). The interaction between inadequate dietary intake and enteric infections may impair gut and immune functions and can lead to and/or exacerbate pre-existing undernutrition (12).

The first 1000 days of life, from conception until the child's second birthday, constitute a critical window for child growth and development when rapid maturation of metabolic, endocrine, neural, and immune systems occurs, according to the Developmental Origins of Health and Disease (13). Birth cohort studies have consistently demonstrated that the first 1000 days are the period of greatest vulnerability to undernutrition (14), and that undernutrition during this period has profound irreversible effects with limited capacity for catch-up growth (15). The high prevalence and burden of child undernutrition confirm the need to scale up interventions during this vulnerable window, including promotion of optimal age-specific IYCF practices (11, 16).

The human gut microbiota, which refers to the ecological community of commensal, symbiotic, and pathogenic microorganisms in the gastrointestinal tract (17), is established during the first 2–3 y of life (18). A growing body of evidence has linked disruptions in the establishment and maturation of the gut microbiota to child undernutrition (19–22). Gut microbiota disruptions in early life might result from adverse environmental insults, such as suboptimal IYCF, and contribute to lifelong and intergenerational deficits in growth and development (23). Although several studies have examined the effects of breastfeeding on the gut microbiota (24–28) and risk of undernutrition (29, 30), few have focused on the effects of the following stage of IYCF: complementary feeding (CF). The aims of this paper are to review the evidence for the relation between CF and undernutrition and to highlight the potential of the gut microbiota to be a promising target in this relation.

## Methods

PubMed was searched using combinations of the following keywords: complementary feeding or complementary food or solid feeding or solid food (SF) and gut microbiome or gut microbiota for the section on the changes in the gut microbiota during the CF period. The search yielded

studies in high-income countries (HICs) not LMICs. For the following section on the gut microbiota and undernutrition, we searched for the papers that proposed a novel approach to describe the disrupted gut microbiota as immature. We also reference a number of papers that describe other definitions of a disrupted gut microbiota. In the last section, based on the definition of the immature gut microbiota, we searched for articles on CF interventions that specifically target the gut microbiota for undernutrition management. As for our selection criteria, we included primary research studies if they 1) were conducted in humans (but we describe an illustrative animal study that enhanced our understanding of the human research); 2) collected (the majority of) fecal samples from infants/children during or around the CF period; 3) examined the effects of CF on the gut microbiota rather than the inherent variation in the process of microbial succession associated with age; 4) examined undernutrition in any of its 3 anthropometric forms (stunting, wasting, underweight); and 5) used next-generation sequencing techniques for microbiome analysis.

## Current Status of Knowledge

### Inadequate CF practices increase susceptibility to undernutrition

The WHO defines CF as “the process starting when breast milk alone is no longer sufficient to meet the nutritional requirements of infants, and therefore other foods and liquids are needed along with breast milk” (31). The transition process from milk-based diets to solid, semi-solid, and soft food and liquids other than milk typically covers the period between 6 mo and 2 y of age (31). Infants have high nutritional needs for their rapid growth, so optimal CF practices are essential to provide key nutrients to maintain healthy growth and development (32). However, unlike the WHO's recommendation for exclusive breastfeeding for the first 6 mo (33), there is no single recommendation for CF. CF encompasses several dimensions including the age of introduction, amount, energy density, nutrient content, frequency of consumption, food consistency, safe preparation and storage of complementary food, and responsive feeding (34).

In 2003 and 2005, the WHO published detailed guiding principles covering the CF dimensions among breastfed (34) and non-breastfed infants (35), respectively. The guiding principles have had an important impact on policies especially in LMICs and have increased attention to nutrition and growth during the CF period (36). Afterwards, in 2008, the WHO used 10 existing datasets from Africa, Asia, and Latin America to define and validate a set of 8 core and 7 optional indicators to assess IYCF based on the guiding principles (37). Five of the 8 core indicators focus on specific dimensions of CF including age of introduction, energy and nutrient content, and frequency of consumption of the complementary food (Table 1), while the remaining 10 indicators relate to breastfeeding. Other dimensions of CF such as adequate consistency and texture

**TABLE 1** Indicators to assess complementary feeding adequacy<sup>1</sup>

Indicators	Definition	Notes
1. Timely introduction to solid, semi-solid, or soft foods	Proportion of infants 6–8 mo of age who receive solid, semi-solid or soft foods	—
2. Minimum diet diversity	Proportion of children 6–23 mo of age who receive foods from 4 or more of the 7 food groups	The 7 food groups are: grains, roots, and tubers; legumes and nuts; dairy products; flesh foods; eggs; vitamin A-rich fruits and vegetables; other fruits and vegetables.
3. Minimum meal frequency	Proportion of children 6–23 mo of age who receive solid, semi-solid, or soft foods (but also including milk feeds for non-breastfed children) the minimum number of times or more according to the infant's age	The minimum number of times is defined as: 2 times/d for 6–8 mo-old breastfed infants; 3 times/d for 9–23-mo-old breastfed children; 4 times/d for 6–23-mo-old non-breastfed children.
4. Minimum acceptable diet	Proportion of children 6–23 mo of age who had at least the minimum dietary diversity and the minimum meal frequency	This is a summary or composite indicator of the previous 2 indicators.
5. Consumption of iron-rich or iron-fortified foods	Proportion of children 6–23 mo of age who receive an iron-rich food or iron-fortified food that is specially designed for infants and young children, or that is fortified in the home	Suitable iron-rich or iron-fortified foods include flesh foods, commercially fortified foods specially designed for infants and young children that contain iron, or foods fortified in the home with a micronutrient powder containing iron or a lipid-based nutrient supplement containing iron.

<sup>1</sup>All indicators are assessed based on the child's dietary intake in the day preceding the survey. Source: WHO (37).

of food and responsive feeding were deemed too complex to assess and require more work to develop valid and reliable indicators (37).

The indicators have been used to assess CF practices worldwide, especially in LMICs. The first published application of the indicators appeared in the country profiles by the WHO using 2002–2008 Demographic and Health Survey (DHS) data from 46 countries (38). Most countries had grossly inadequate CF practices, especially those in South Asia and sub-Saharan Africa with the highest prevalence and burden of child undernutrition (4). In a more recent analysis of the UNICEF global database of national-level household surveys of 85 countries conducted between 2010 and 2016, CF practices were still poor worldwide and were the poorest in the aforementioned 2 regions (39). Specifically, <50% of children in South Asia and sub-Saharan Africa achieved minimum meal frequency, <25% achieved minimum diet diversity, and <15% achieved a minimum acceptable diet.

Other than assessing CF practices, the WHO indicators have been used to examine the associations between CF and undernutrition susceptibility in different populations in LMICs (40–46), demonstrating the applicability of the indicators for their intended purposes and in populations for whom they were originally developed (37). In Malawi, for example, a sub-Saharan African country severely burdened by child undernutrition (47), 13- to 23-mo-old children who did not meet the minimum meal frequency or the minimum acceptable diet indicators were more likely to be underweight (45). In Bangladesh, which has one of the highest burdens of child undernutrition worldwide (48) and where CF practices remain grossly inadequate (49), untimely introduction of complementary food and failure to meet the minimum diet diversity indicator were associated

with stunting among 6- to 23-mo-old children (46). An association between the consumption of a diverse diet and lower likelihood of stunting was also noted in a pooled analysis of 74,548 children aged 6–23 mo using the 2010–2014 DHS from 39 LMICs (50). In addition, consumption of animal-source food, which is not currently a WHO indicator but has emerged as a critical dimension related to protein quality (36), was inversely associated with stunting after adjustment for socioeconomic and other covariates (50).

CF interventions that are effective at reducing undernutrition in LMICs are a high priority (51). Systematic reviews and meta-analyses assessing the effectiveness of CF interventions are valuable, yet variations in study populations, type of interventions, reported outcomes, and grade quality of the reviewed studies render calculation of pooled estimates challenging. Heidkamp (52) synthesized the evidence in 2017 from recent systematic reviews and meta-analyses of the impact of CF interventions on linear and ponderal growth of children aged 6–23 mo in LMICs (53–55). The systematic reviews of interventions with CF education alone (53, 55) and those of interventions with provision of food and other supplements with or without education (54, 55) revealed modest effects on height and weight gain. In another review, CF education and supplementary feeding interventions did not have significant effects on stunting and wasting prevalence, whereas CF provision had significant positive effects on the prevalence of stunting (56). Other systematic reviews have noted similar small and mixed effects of CF interventions on child growth in LMICs (57, 58).

The associations between the multiple dimensions of CF and undernutrition coupled with the limited catch-up growth following CF interventions in undernourished

children highlight the complexity of this relation. Further, adequate CF to maintain child growth and development depends not only on what, when, and how children are fed but also on the extent to which their body is capable of efficiently digesting, absorbing, and utilizing these foods (23), 3 functions in which the gut microbiota plays a critical role.

### Significant changes in the gut microbiota of children occur during the CF period

The gut microbiota develops and matures toward an adult-like configuration during the first 2–3 y of life (18). Gut microbiota development has prominent effects on long-term health (23) and is affected by several factors, including mode of delivery, antibiotic exposure, and IYCF (24, 25, 27). While the differential effects of milk-based diets (breast vs. formula vs. mixed feeding) on the infant microbiota have been examined (24–28), less research has been conducted on the effects of CF (59). Further, some studies have suggested that breastfeeding in terms of exclusivity, amount, duration, and cessation is the main driver of the changes in the gut microbiota during the CF period rather than CF itself (24, 25). The following section reviews the studies (Table 2) examining the association of CF with the changes in the gut microbiota and addresses whether the aforementioned breastfeeding-related variables influence these changes.

Prospective cohort studies with multiple fecal sample collections during the CF period help inform how the introduction to new food components influences the changes in the gut microbial structure and function in early life. Introduction of SF among infants in the United States was associated with increased  $\alpha$ -diversity (within sample diversity) as well as changes in the composition of bacterial taxa and predicted function, with observed differences by exclusive breastfeeding status prior to SF introduction (60). Specifically,  $\alpha$ -diversity was higher following SF introduction in infants who were not previously exclusively breastfed compared with those who were. SF introduction was associated with overrepresentation of 24 functional genes in exclusively breastfed infants compared with 230 functional genes in non-exclusively breastfed infants. The changes in predicted function following SF introduction were corroborated by a metagenomic analysis of the gut microbiome of a full-term, vaginally delivered, healthy, and exclusively breastfed boy (61). The boy's microbiome was enriched with functional genes characteristic of the adult gut microbiome including genes for vitamin biosynthesis, plant polysaccharide utilization, and breakdown of xenobiotic compounds (foreign substances to the human body; e.g., antibiotics, pharmaceuticals). Further, fecal concentrations of individual SCFAs (acetate, propionate, and butyrate) were higher following introduction of table food. However, since this was a case study of 1 child, it is important to replicate the results among a larger number of infants.

The effect of the age of introduction and the composition of the complementary food on the gut microbiota of infants

and children have been also studied. Pannaraj et al. (62) examined the trajectory of microbiota maturity among US infants using a random forest (RF) model, which is a machine-learning algorithm suggested by Subramanian et al. (63) to determine a ranked list of all bacterial taxa in the order of age-discriminatory importance. Early CF (<4 mo) compared with later CF ( $\geq 4$  mo of age) was associated with a rapid maturation of the gut microbiota and increased predicted function related to xenobiotics biodegradation and metabolism. In the Nurture cohort study, early ( $\leq 3$  mo) versus late ( $> 3$  mo) CF was associated with higher  $\alpha$ -diversity and differential abundance of 29 bacterial taxa at 3 and 12 mo of age after adjusting for potential confounders including breastfeeding (64). Early CF was also associated with greater concentrations of fecal butyrate and total SCFA concentrations at 12 mo.

Unlike the studies conducted among infants in the United States, a study by Laursen et al. (65) among Danish infants suggested that the age of SF introduction (3–6 mo) was not associated with  $\alpha$ -diversity or microbiota composition at 9 mo. Nevertheless, the duration of exclusive breastfeeding, which was  $\leq 6$  mo among all infants, was associated with these microbiota indicators. The authors concluded that exclusive breastfeeding duration, rather than CF timing, was a stronger determinant of the gut microbiota in early life. Studies by Backhed et al. (24) among Swedish infants and Stewart et al. (25) among infants and children in 3 European countries (Germany, Sweden, and Finland) and US states (Colorado, Georgia, and Washington) had a similar conclusion. They argued that breastfeeding cessation rather than SF introduction is the major driver in the development of an adult microbiota. It is worth noting, however, that these studies (24, 25) based their conclusion on the effects of breastfeeding status and did not examine the effect of the CF dimensions, such as age of introduction and composition of SF, on the infants' microbiota.

To decipher the effect of breastfeeding versus that of CF, Laursen et al. (66) stratified the Danish infants by breastfeeding status at 9 mo. They found that protein and fiber content of SF and progression toward family food were associated with higher  $\alpha$ -diversity in both groups of infants, suggesting that these changes were independent of breastfeeding status. Additionally, whereas meat, cheese, and rye bread represented the specific food groups most strongly associated with  $\alpha$ -diversity among all infants as well as those no longer breastfed at 9 mo, porridge (primarily oatmeal) was most strongly associated with  $\alpha$ -diversity among infants still breastfed. Progression to family food was associated with a decrease in the abundance of several bacterial genera, including *Bifidobacterium*, and an increase in the abundance of others, including *Faecalibacterium* and *Ruminococcus*, among all infants (65). Of note, *Bifidobacterium* is known for its capacity to utilize lactose and human-milk oligosaccharides in breast milk (67) and has been referred to as a “milk-oriented” taxon in the study by Gehrig et al. (68). *Faecalibacterium* and *Ruminococcus*, on the other hand, increase with the addition of dietary

**TABLE 2** Summary of the studies examining the changes in the gut microbiota during the CF period<sup>1</sup>

Reference	Study design	Study location	Sample size, n	Age at fecal sample collection	Examined variable related to CF	Examined effect of BF in relation to CF	Examined variable related to the gut microbiota				
							α-Diversity	Microbial composition	Fecal SCFAs	Functional genes	Relative microbiota maturity <sup>2</sup>
Thompson et al., 2015 (60)	Prospective cohort	Atlanta, USA	9	Periodically between 13 d and 14 mo	Introduction (4–6 mo)	✓	✓	✓	7	✓ <sup>3</sup>	7
Koenig et al., 2011 (61)	Case study	USA	1	Periodically between birth and 2.5 y	Introduction (~5.5 mo)	✓	✓	✓	✓	✓	7
Pannaraj et al., 2017 (62)	Prospective cohort	California and Florida, USA	119	Periodically between 1 and 331 d	Introduction (4–6 mo) and age of introduction (<4 vs. ≥4 mo)	✓	✓	✓	7	✓ <sup>3</sup>	✓
Differding et al., 2020 (64)	Prospective “Nurture” cohort	North Carolina, USA	67	At 3 and 12 mo	Age of introduction (≤3 vs. >3 mo)	✓	✓	✓	✓	7	7
Laurson et al., 2016 and 2017 (65, 66)	Prospective cohort	Denmark	227	At 9 and 18 mo	Age of introduction (3–6 mo) and composition	✓	✓	✓	7	7	7
Qasem et al., 2017 (69)	Randomized controlled trial	Manitoba, Canada	87	Before and after introduction between 4 and 6 mo in 56 infants	Introduction (4–6 mo) and composition	✓	✓	✓	7	7	7
Krebs et al., 2013 (70)	Randomized controlled trial	Colorado, USA	45	Monthly between 5 and 9 mo in 14 infants	Introduction (5 mo) and composition	✓	✓	✓	7	7	7

<sup>1</sup>BF, breastfeeding; CF, complementary feeding.

<sup>2</sup>Calculated using a random-forest model which is a machine-learning algorithm to determine a ranked list of all bacterial taxa in the order of age-discriminatory importance.

<sup>3</sup>Predicted functional genes.



fiber or protein to the diet (71, 72) and have been thus referred to as “weaning-phase” taxa. Hence, the changes in the gut microbiota during the CF period are likely to be driven by a combination of breastfeeding- and CF-related variables.

Randomized controlled trials examined the effects of CF on the gut microbiota of infants. Eighty-seven exclusively breastfed infants were randomly assigned to receive either iron-fortified cereal, iron-fortified cereal with fruit, or meat as their first complementary food (69). The age of SF introduction varied by the parents’ preference and ranged between 4 and 6 mo, but all infants consumed their assigned diets for 2–4 wk. In a subset of 56 infants, gut microbiota analysis revealed increased  $\alpha$ -diversity following introduction of meat or cereal with fruit, but not cereal alone. No significant changes in gut microbiota composition were noted after introduction of any of the SFs. In another trial, 45 exclusively breastfed 5-mo-old infants were randomly assigned to receive commercially available pureed meats, iron- and zinc-fortified infant cereals, or iron-only fortified infant cereals as the first and primary complementary food through 9–10 mo of age (70). In a subsample of 14 infants, no significant change in  $\alpha$ -diversity was observed following introduction of any SF. Changes in gut microbiota composition were apparent among infants introduced to the iron-fortified cereal compared with those introduced to the meat or iron- and zinc-fortified cereal.

The studies in this section suggest that significant changes in the gut microbiota occur during the CF period and are potentially driven by breastfeeding as well as CF. All the studies were conducted in HICs. No similar studies were conducted among LMIC populations, which are the focus of this review, or in the context of undernutrition in which other factors including deficient diets, EED, and poor sanitation might also drive the changes in the gut microbiota during the CF period. Moreover, none have examined the effect of CF adequacy as assessed by the WHO indicators on the gut microbiota. More research is needed to understand 1) the nature and magnitude of the link between CF and the gut microbiota, 2) the extent to which such a link can be beneficial to improve children’s growth and nutrition, and 3) the means in which the knowledge gained from items “1” and “2” can translate to the context of undernutrition and LMICs.

### **Gut microbiota disruptions are associated with, and can even cause, child undernutrition**

Disruptions in the gut microbiota in early life are likely to have detrimental effects on children’s nutritional status and health later in life. Studies linking the gut microbiota to undernutrition have different definitions for gut microbiota disruptions. One novel approach, described in this section, was proposed by Jeffrey Gordon’s team who suggested that undernourished children have immature gut microbiotas (63, 73–75). Such an approach provides potential insight and testable hypotheses on the role of the gut microbiota in child

undernutrition and informs the development of promising interventions.

Smith et al. (74) studied 317 Malawian twin pairs during the first 3 y of life, some of whom were discordant for kwashiorkor, a form of severe acute malnutrition (SAM) characterized by peripheral edema, abdominal distension, and hepatic metabolic disruptions (76). Twin studies are especially valuable in gut microbiota research as they help distinguish the effects of genetic from those of environmental factors. Compared with the gut microbiota of the healthy co-twin, the microbiota of the twin with kwashiorkor was immature and resembled that of younger children (74). Even when the twin with kwashiorkor was treated with ready-to-use therapeutic food (RUTF), an energy-dense and micronutrient-enriched paste used in the treatment of SAM, the divergent trajectory of gut microbiota maturation was not corrected.

To further investigate the role of the gut microbiota in undernutrition, Smith et al. (74) transplanted fecal communities from several discordant twin pairs to C57BL/6J germ-free mice, which lack micro-organisms living in and on them. The recipient mice were fed a typical Malawian diet that is nutrient-deficient and low in calorie density for 3 wk. Mice that received transplants from the kwashiorkor-diagnosed twin lost more weight, had overrepresentation of proinflammatory taxa, and exhibited perturbed metabolism of amino acids and carbohydrates compared with mice with fecal transplants from the healthy co-twin. One proposed mechanism in which the gut microbiota might be implicated in kwashiorkor is through the generation of products such as inhibitors of enzymes in the tricarboxylic acid cycle, which can compromise effective energy metabolism and eventually nutritional status. This proof-of-concept study suggests that an immature gut microbiota coupled with a nutrient-deficient diet may be included among the causal risk factors of undernutrition.

Gut microbiota immaturity was further examined in a study by Subramanian et al. (63) among Bangladeshi children younger than 2 y using a RF machine-learning algorithm. The relative abundance of the operational taxonomic units (sequences that are clustered together based on similarity to inform taxonomy) was regressed against the chronological age of each child at the time of fecal sample collection to identify age-discriminatory taxa. Among the 24 most age-discriminatory taxa were the weaning-phase taxa including *Faecalibacterium prausnitzii* and *Ruminococcus* sp. and the milk-oriented taxa including *Bifidobacterium longum*. Two metrics to assess the microbiota maturity of children were subsequently defined using the sparse 24-taxon model. The first metric, relative microbiota maturity, compared the microbiota age of the child with that of healthy children of similar chronologic age. The second, microbiota-for-age  $z$  score (MAZ), is similar to the anthropometric  $z$  scores used to assess nutritional status such as height-for-age, weight-for-age, and weight-for-height  $z$  scores.

Applying the 24-taxon model to the fecal samples of a group of 64 Bangladeshi children aged 6–20 mo with SAM

revealed that undernourished children had gut microbiota immaturities and lower MAZ compared with age-matched healthy children (63). The microbiota immaturities were only partially repaired when the children with SAM were treated with RUTF or a locally produced alternative, supporting previous findings that existing nutrition therapies fail to completely repair immature gut microbiotas (74). The RF model among Bangladeshi children was applicable to the population of Malawian twin pairs (73) assessed in the study by Smith et al. (74). *F. prausnitzii*, *Ruminococcus* sp., and *B. longum* were also age-discriminatory in the Malawian sparse 25-taxon model (73). In addition, MAZ among Malawian twins at 12 months was significantly positively correlated with weight-for-height *z* scores and weight-for-age *z* scores at 18 mo, suggesting that MAZ may be useful for predicting future ponderal growth.

Although the use of RF models to identify age-discriminatory taxa is helpful, it typically describes a “parts list” as it focuses on the abundance of community members without accounting for the interactions between them (75). Analysis of conserved bacterial taxon–taxon covariance in the gut microbiota of healthy Bangladeshi children younger than 5 y revealed a network of 15 covarying bacteria termed an “ecogroup” (75). *F. prausnitzii* and *B. longum* were among the 15 covarying taxa, along with others that were identified as age-discriminatory in the RF model among Bangladeshi children. The ecogroup confirmed the existence of a program of gut microbial community maturation that was completed by the second year of life in healthy Bangladeshi children. The ecogroup further supported findings that undernourished Bangladeshi children had impaired gut community development characterized by perturbed interactions between the 15 covarying taxa.

Other definitions of gut microbiota disruption have been proposed including lower  $\alpha$ -diversity and/or higher abundance of pathogenic taxa (77, 78). Different forms of undernutrition have been also studied, ranging from chronic undernutrition (79) to moderate acute malnutrition (MAM) (68) and SAM (63, 73, 74). Further, associations between gut microbiota disruptions and undernutrition have been examined using different microbiota analytic methods [e.g., 16S ribosomal RNA (rRNA) 454 pyrosequencing vs. 16S rRNA Illumina sequencing versus shotgun metagenomic sequencing] in various populations residing in different geographic locations with distinct cultural practices and traditional diets. Such variations in definition, analysis, and study population characteristics possibly explain the contrasting results related to the nature and strength of the association between gut microbiota disruption and undernutrition. All of the studies, however, hint at the potential of the disrupted gut microbiota to be a key player in the web of risk factors of undernutrition. Interestingly, the opposite direction of the relation where child undernutrition may cause gut microbiota disruption has been suggested in a few review papers (20, 21) but has not been not fully studied in children or animal models.

### Complementary food targeting the gut microbiota is a promising intervention for undernutrition

With the advancement in our knowledge of the paramount role of gut microbiota disruption in child undernutrition, a number of interventions targeting the gut microbiota have emerged as promising treatment modalities. Prebiotics, probiotics, and synbiotics have gained significant attention following findings of their potential ability to modulate the gut microbiota of undernourished children (80, 81). A systematic review of the effects of probiotics on child growth suggests that probiotics might have more significant effects improving child nutritional status and growth among undernourished children and those living in LMICs (82). There are a number of challenges, however, to implementing probiotic-based approaches, including the need to closely monitor safety, particularly among undernourished children with impaired immune function, and to gain cultural acceptability to supplement children with live micro-organisms (83). Locally produced complementary food that targets gut microbiota immaturities among undernourished children can help overcome such challenges.

Gehrig et al. (68) conducted a pilot randomized controlled trial to compare the efficacy of microbiota-directed complementary food (MDCF) with the traditional rice- and lentil-based ready-to-use supplementary food (RUSF) used in the treatment of MAM. The 1-mo pilot trial tested 3 MDCF formulations with different proportions of 4 ingredients—peanut flour, chickpea flour, soy flour, and banana—among 12- to 18-mo-old Bangladeshi children with MAM. The ingredients were selected based on their growth-promoting effects in gnotobiotic mice and piglets (animals with defined microbial communities) colonized with members of the gut microbiota from undernourished Bangladeshi children. MDCF-1 had all 4 ingredients but at lower concentrations than MDCF-2, and MDCF-3 had chickpea flour and soy flour only. MDCF-1 and RUSF contained milk powder. All MDCF formulations were supplemented with a micronutrient mixture designed to provide 70% of the recommended daily allowances for 12- to 18-mo-old children. The MDCF formulations and RUSF had similar protein-energy ratio, fat-energy ratio, and macro- and micronutrient content and provided 250 kcal/d.

At the end of the trial, all children had improved weight-for-height *z* scores regardless of the treatment group ( $n = 14$ – $17$  children per group) (63). Children randomly assigned to MDCF-2, compared with MDCF-3, had a significantly greater increase in midupper arm circumference, an independent diagnostic criterion of MAM (84). Further, MDCF-2 induced an increase in the relative abundance of several weaning-phase taxa including *F. prausnitzii* and a decrease in that of milk-oriented taxa such as *B. longum* compared with the 3 other treatments. However, there was no improvement in MAZ with any of the treatments, which the authors attributed to the possible confounding by unexpectedly high baseline microbiota maturity scores in the children with MAM in this study (63). MDCF-2 was uniquely associated

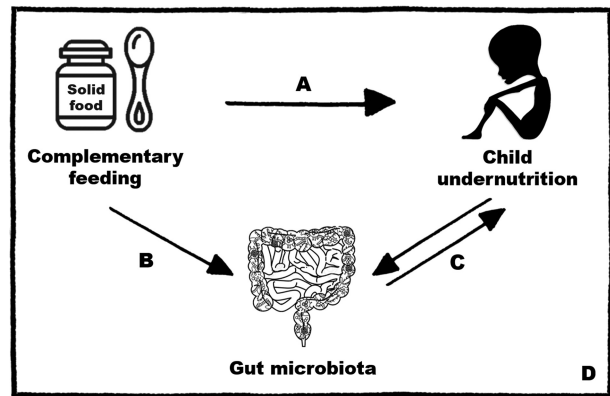
with covariation of the ecogroup taxa towards a more complete community repair (75). MDCF-2 also increased the abundance of proteins that are higher in plasma from healthy children and that are positively correlated with height-for-age *z* scores, and it reduced the concentrations of proteins elevated in plasma of undernourished children and those that are negatively correlated with height-for-age *z* scores (63). Therefore, despite the small group size and the short length of the study, MDCF-2 elicited a marked shift in the microbiota profiles and plasma proteome toward those of healthy children.

Findings from this pilot trial informed the design and implementation of a proof-of-concept efficacy trial, whose protocol has been recently published (85) with similar aims but among a larger group of 248 Bangladeshi children with MAM for a longer 3-mo period. Another study protocol has been published for the MALINEA (Malnutrition et Infection de l'Enfance en Afrique) project, which aims to compare the effects of 3 strategies of re-nutrition for MAM on the gut microbiota of 840 children aged 6–24 mo old in 4 African countries (Madagascar, Niger, Central African Republic, and Senegal) (86). The children are randomly assigned to receive enriched flour alone, enriched flour with prebiotics (combination of inulin and fructo-oligosaccharides), or enriched flour coupled with a 4-d antibiotic treatment (azithromycin) for 12 wk. It is hoped that results from these studies will serve as a stepping stone for the development of complementary food targeting the microbiota of undernourished children for sustainable benefits on child growth.

### Conclusions and Future Research

The persistent high prevalence of child undernutrition in LMICs and its long-term health and societal costs are a call for action. This review paper provides evidence supporting a plausible relation between CF, the gut microbiota, and child undernutrition (Figure 1). An association between inadequate CF and child undernutrition was suggested in numerous studies in different LMICs. In contrast, studies examining the changes in the gut microbial composition and function during the CF period were largely conducted in HICs. Further, a disrupted gut microbiota has been associated with, and causally linked to, child undernutrition. Indeed, the direction of the causality is not fully examined and potentially exists in both directions depending on genetic and environmental conditions. The current state of knowledge supporting the potential of the gut microbiota to be a key player in the relation between CF and undernutrition has ignited interest in developing microbiota-directed interventions during the CF period for undernutrition management.

More research is needed to further our knowledge of the interplay between the different dimensions of CF and the gut microbiota, especially among populations in LMICs, and to inform an update of the WHO guiding principles and indicators of IYCF that were published over a decade ago (22). Research is also necessary to decipher the mechanisms



**FIGURE 1** Summary of the plausible links between CF, the gut microbiota, and child undernutrition. (A) Inadequate CF is associated with child undernutrition. These associations were mostly examined in LMICs. CF interventions often have limited effects on child growth, hinting at the complexity of the relation between CF and undernutrition. (B) Significant changes in the gut microbiota occur during the CF period. The introduction of new food components and the age of introduction and composition of the complementary food influence the gut microbiota. However, evidence in this area originates solely from HICs. (C) Gut microbiota disruptions are associated with, and causally linked to, child undernutrition. A bidirectional relation is plausible where a disrupted gut microbiota can cause undernutrition and vice versa. (D) Interventions for undernutrition targeting the gut microbiota during the CF period are promising. More research is needed to further our knowledge of the interplay between CF, the gut microbiota, and undernutrition as this can help better inform the design of interventions with long-lasting benefits to combat child undernutrition and promote health and well-being. CF, complementary feeding; HIC, high-income country; LMIC, low- and middle-income country.

involved in the association between inadequate CF and undernutrition, including those related to the microbial communities residing in the child's gut. Studies using animal models and those conducted among children in LMICs can address how CF and the gut microbiota influence growth and will contribute to the development of an updated algorithm of the risk factors of undernutrition. The potential of the disrupted gut microbiota as a key player in this algorithm is evident. Such a holistic view of the risk factors of undernutrition can help better inform the design of interventions to create persistent beneficial effects on the maturation process of the gut microbiota and child growth. This, in turn, can help decrease the prevalence and burden of undernutrition and promote health and well-being.

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