

Early-life gut microbiome assembly in low- and middle-income countries: Interactions between undernutrition, infection, and environmental enteric dysfunction

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ABSTRACT

The uninterrupted assembly of the early-life gut microbiome is central to growth, immune maturation, and resistance to infection. In low- and middle-income country (LMIC) settings, this process is often disrupted by nutritional inadequacy, high enteropathogen exposure, and health-system constraints, resulting in increased vulnerability to undernutrition and environmental enteric dysfunction (EED). These pressures interact bidirectionally as undernutrition and EED can impair intestinal barrier function and alter microbial composition and function, while recurrent infection and inflammation further reduce nutrient absorption and perpetuate microbiome perturbations. Here, we summarise current evidence on early-life microbiome assembly in LMIC settings, how wasting, stunting, micronutrient deficiencies and EED influence microbial community composition and function, how infection and microbiota perturbations reciprocally reinforce one another, and the implications of these interactions for microbiome-directed interventions. We highlight that nutritional rehabilitation alone may be insufficient when inflammation and enteropathy persist, whereas emerging microbiota-directed complementary foods and related microbiome-targeted approaches offer a mechanistically informed route to promoting microbiome maturation and improving growth outcomes. Finally, we outline key evidence gaps, particularly geographic under-representation and the limited availability of longitudinal, multi-omic studies, which constrain the development of generalisable diagnostics and scalable interventions.

1. Introduction

The gut microbiome is a complex microbial community of bacteria, viruses, archaea and micro-eukaryotes that inhabit the gastrointestinal tract [1]. Its composition varies substantially between individuals and is shaped by early-life exposures, diet, environment and host factors [2–5]. Beyond taxonomic diversity, the microbiome plays fundamental roles in host metabolism by fermenting complex carbohydrates into short-chain fatty acids (SCFAs), producing bioactive metabolites, and modulating nutrient availability [6–9]. It also contributes to immune development and colonisation resistance against enteric pathogens [10–12]. Many of these functions are established during the first 1000 days, a critical window for microbiome development and long-term health.

This review examines early-life gut microbiome development in low- and middle-income (LMIC) settings and its links to malnutrition,

infections, and environmental enteric dysfunction (EED) [5,13]. Compared with high-income settings, LMICs experience a substantially higher burden of pathogen exposure, undernutrition, and EED, all of which influence microbiome development and contribute to poor child health outcomes. Interactions between nutrition, infection, and the gut microbiome are bidirectional and can become self-reinforcing, driving growth faltering and increasing disease susceptibility in early life [14].

As summarised in Fig. 1, malnutrition, infection, EED, and microbiome development are interconnected through reciprocal pathways. Nutrient limitation and enteropathy can alter microbial community structure and function, impair epithelial barrier integrity, and compromise immune responses. In turn, infection and inflammation can reduce dietary intake, impair nutrient absorption, and further perturb microbial ecosystems. In environments characterised by persistent pathogen exposure, repeated antibiotic use, and limited capacity for microbiome

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and mucosal recovery, these processes can become self-perpetuating, exacerbating undernutrition and poor health [14].

We first summarise early-life microbiome assembly in LMIC settings and the key environmental and biological factors that shape this trajectory. We then examine how undernutrition and EED disrupt microbiome composition and function, placing these changes within mechanistic pathways that contribute to growth faltering. Finally, we discuss how infection and microbial ecosystem perturbations can reinforce one another, review current microbiome-directed interventions, identify key knowledge gaps, and outline priorities for future research, policy and practice.

2. Early-life gut microbiome in LMICs

The first 1000 days of life represents a critical period for immune maturation and microbiome assembly, with lasting implications for metabolic health and disease susceptibility [15,16]. During this period, the gut microbiome develops rapidly through interactions between host biology, diet, and environmental exposures. Although the overall trajectory of microbiome assembly is relatively conserved across populations, its composition, timing and stability differ substantially between infants living in LMICs and high-income countries (HICs) [17]. These differences reflect distinct nutritional, infectious and environmental pressures that influence microbial colonisation, ecological succession and microbiome resilience [17,18].

Microbiome assembly is shaped before and immediately after birth by maternal health and the perinatal environment. Although the foetus develops *in utero* under largely sterile conditions during uncomplicated pregnancies, maternal nutrition, infection and environmental exposures, influence foetal development and establish the intestinal environment into which postnatal microbial colonisation occurs [19–21]. In LMIC settings, maternal undernutrition, micronutrient deficiencies and infectious diseases are more prevalent, and may alter maternal microbial metabolism, metabolite transfer and vertical microbial transmission [22]. Consistent with this, maternal gut microbiome composition has been reported to predict birth weight more strongly than gestational age, highlighting the importance of maternal microbial health for infant development [22,23].

Gestational age is another major determinant of microbiome assembly. Preterm infants (<37 weeks' gestation) have an underdeveloped intestinal barrier, a more oxygenated gut environment, and

increased exposure to intensive clinical care, all of which can delay colonisation by anaerobes like *Bifidobacterium*, *Bacteroides* and *Atopobium* [24–27]. As maternal undernutrition increases the risk of pre-term birth, these microbiome alterations may be particularly relevant in LMIC settings, where prematurity and low birth weight remain common [28,29]. These outcomes contribute substantially to infant mortality and to long-term risks of infection, chronic disease, and impaired physical and cognitive development. In 2020, an estimated 19.8 million infants worldwide were born with low birth-weight (LBW) with an estimated 5.5 million pregnant and lactating women suffering from malnutrition across 12 crisis-affected countries, which increased to 6.9 million in 2022 [30–33]. The burden was highest in South Asia, primarily India and Bangladesh, where prevalence may approach 30% in some settings, while sub-Saharan Africa also has elevated rates, generally around 12% and reaching 15% in some areas [31]. As LBW and prematurity are themselves associated with altered microbial colonisation and increased clinical vulnerability, they represent an important pathway through which maternal nutritional disadvantage may shape early-life microbiome assembly.

Delivery mode and infant feeding further influence early microbial succession [34,35]. Vaginal delivery promotes transmission of maternal microbes, whereas Caesarean (C)-section delivery is consistently associated with reduced abundance of *Bacteroides* and *Bifidobacterium*, and altered ecological succession that may persist well beyond infancy [35–38]. C-section rates are not determined by national income alone, but by a mixture of medical, cultural, demographic, and policy factors [39]. In East Asia, North America, and parts of Europe, increasing maternal age has contributed to rising C-section rates, whereas in settings such as Egypt and parts of South America, very high rates may also reflect structural incentives within healthcare systems that favour surgical delivery [39,40]. By contrast, due to increased risk of surgery, rates in sub-Saharan Africa often remain close to 5%, below the 10–15% range often discussed in relation to unmet obstetric need [39,40]. As delivery mode influences the infant's earliest microbial exposures, both overuse and under-access to C-section may be relevant to how healthcare systems shape microbiome assembly in different settings.

Post-delivery breastfeeding supports the expansion of *Bifidobacterium* through the provision of human milk oligosaccharides (HMOs) [38, 40–45]. However, the composition of human milk is itself influenced by maternal nutritional status, health, and environmental exposures, leading to variation in the concentrations of HMOs, micronutrients,

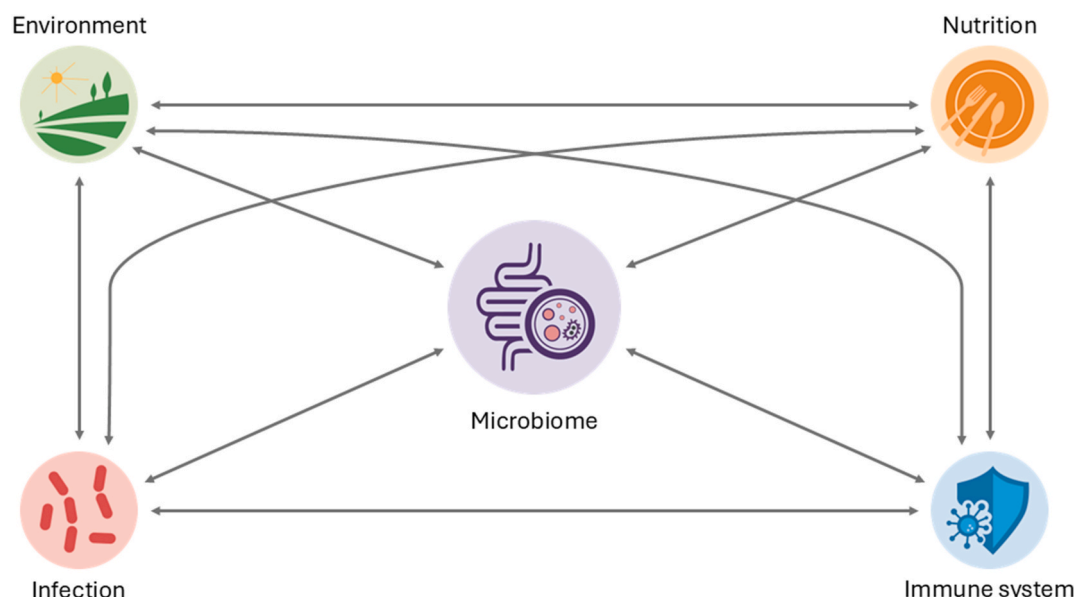


Fig. 1. Schematic of multivariate interactions linking the gut microbiome, nutrition, infection and EED.

immune factors and other bioactive components that shape infant gut microbiome development [46]. In contrast, formula feeding is generally associated with increased abundance of spore-forming *Clostridia* and other taxa with greater pathogenic potential [41]. Although these relationships are observed globally, their impact in LMICs is shaped by regional variation in breastfeeding practices, complementary feeding, healthcare access and nutritional status. The World Health Organisation (WHO) recommends exclusive breastfeeding for the first six months of life to achieve optimal health outcomes [47]. While breastfeeding rates are often higher overall in LMICs than in high-income countries (HICs), substantial regional heterogeneity exists; for example, exclusive breastfeeding rates are generally lower in West Africa than in East Africa [48]. At the same time, many LMIC settings also show relatively high rates of early complementary feeding that is either driven by necessity, food insecurity, or cultural practice [49].

Complementary feeding is usually introduced between 6 and 24 months of age, but early introduction can lead to sub-optimal outcomes [49]. Before 6 months of age, the infant gut and immune system remain developmentally immature, increasing susceptibility to infection from contaminated foods and possibly inflammation and malabsorption, if foods cannot be adequately digested [49]. In many settings, complementary foods such as maize porridge are substantially less nutrient-dense than breastmilk, potentially contributing to nutrient displacement and undernutrition [49]. Conversely, where introduced foods are calorie-dense and rich in added sugars such as processed cereals, early complementary feeding may contribute to inappropriate weight gain and increase later life obesity risk. This is, however, more common in urban and mid-to high-income scenarios [49]. Complementary feeding patterns are therefore not only relevant to nutrition, but also to the substrates and exposures that shape microbiome development during such a critical window.

One characteristic feature of microbiome development in many LMIC populations is the persistence of taxa adapted to traditional diets and higher environmental microbial exposure. *Bifidobacterium longum* subsp. *infantis*, which efficiently metabolises HMOs [50], often remains highly prevalent during early infancy and exhibits greater strain diversity than is typically observed in HIC populations [50]. Enhanced HMO utilisation capacity suggests that breastmilk may play a more prominent nutritional role in populations in which *B. longum* subsp. *infantis* predominates [50]. This is supported by the Joint Child Malnutrition Estimates highlighted above, which report higher breastfeeding prevalence across many LMICs [48]. Furthermore, the ability of *B. longum* subsp. *infantis* to metabolise plant-derived glycans, coupled with its extensive HMO utilisation repertoire, is consistent with coexistence of prolonged breastfeeding and complementary feeding practices [50]. Infants in LMICs may also harbour higher early-life abundance of *Escherichia coli*, likely reflecting increased exposure to environmental microorganisms [51,52]. During weaning, microbial diversity rapidly increases as the microbiome transitions towards an adult-like profile. In many LMIC settings, fibre-rich complementary diets favour expansion of members of the phylum Bacillota (formerly Firmicutes) and the genus *Segatella* (formerly classified within *Prevotella*), whereas animal protein-rich diets more commonly associated with HICs favour *Bacteroides* dominance [53,54]. *Segatella copri* is typically one of the most prominent species within non-westernised microbiomes [55]. It is commonly associated with diets rich in dietary fibres, plant-derived complex carbohydrates, and resistant starch, reflecting its extensive carbohydrate-utilisation capacity [55]. Tett et al. reported that members of the *S. copri* complex were detected in 95.4% of non-westernised samples, in some cases accounting for more than 50% of the total community abundance, compared with 29.6% of westernised samples [55]. These observations suggest that dietary patterns are a major factor underpinning the contrasting prevalence of *S. copri* across populations.

Despite these characteristic features, microbiome maturation in LMICs is frequently disrupted by recurrent nutritional and infectious challenges. Compared with infants in HICs, microbiomes are often

slower to mature, show reduced ecological stability and harbour a greater abundance of opportunistic pathogens and antimicrobial resistance (AMR) determinants [56]. Repeated enteropathogen exposure, antibiotic use, intestinal inflammation and impaired nutritional status can limit recovery following perturbation, resulting in persistent alterations to microbial community structure and function. These cumulative disturbances provide the biological context in which malnutrition, EED and recurrent infection interact to drive growth faltering and poor child health outcomes [36,57–59].

Infants are commonly colonised by at least one potentially pathogenic bacterium by three months of age, and exposure risk increases further with crawling, mouthing behaviour, and the introduction of solid food [60]. Although much of this carriage is asymptomatic, it leaves children vulnerable to infection if host immunity or microbiome resilience is compromised [60]. More importantly, repeated pathogen exposure may drive chronic inflammation, particularly in settings with poor water, sanitation and hygiene (WASH) [60]. Recent work also suggests animal faeces may represent an important and sometimes underappreciated source of exposure in LMIC contexts, as domestic livestock, free-roaming poultry, cats and dogs often live in close proximity to human living and sleeping spaces [61]. These sustained exposures may accelerate progression towards EED.

Repeated infection and perceived infection risk also drive increased antibiotic use, which can further disrupt the microbiome and promote AMR. In many LMIC settings, high antibiotic exposure reflects both the elevated burden of neonatal sepsis and broader structural factors, including poor diagnostic capacity and unregulated over-the-counter access. This is particularly evident in parts of South Asia and sub-Saharan Africa, where a significant proportion of infants are exposed to broad spectrum antibiotics before 6 months of age [62]. Antibiotic exposure during this early period may markedly reduce *Bifidobacterium*, a key genus in early microbiome assembly, with potential consequences for immune training and for digestion of milk and HMOs [63].

Child malnutrition remains a major global health challenge, with an estimated 150 to 200 million children under 5 affected by some form of malnutrition, with most of these being in LMICs [48,64]. Although prevalence has declined gradually in recent decades, faster reductions would yield substantial health benefits [48,64]. Stunting, defined as low height-for-age, remains the most common form of undernutrition (Fig. 2), while wasting, defined as low weight-for-height, is less prevalent but more severe (Fig. 3). Although both have decreased over time, this progress is increasingly complicated by rising levels of child overweight and overnutrition, in some settings [48]. The overlap between undernutrition and socioeconomic disadvantage is reflected in the global distribution of stunting and wasting (Figs. 2 and 3).

Together, these interconnected LMIC-associated exposures contribute to microbiome trajectories that are often slower to mature and more vulnerable to perturbation by inflammation, antibiotics, and enteropathogen pressure. Socioeconomic disadvantage acts through upstream determinants including diet quality, household crowding, sanitation infrastructure and access to timely and appropriate healthcare, creating an exposure landscape that increases the risk of malnutrition and EED. These conditions not only impair nutrient absorption but also further disrupt microbiome development, establishing a self-reinforcing cycle that contributes to growth faltering. Although, country income classifications provide only a coarse proxy for these constraints and substantial within-country heterogeneity exists, a socioeconomic framing remains valuable because it captures the broader nutritional, infectious, and iatrogenic pressures within which microbiome assembly and recovery occurs [65–67]. Consequently, LMIC settings are best understood not simply as geographic categories, but as environments characterised by intersecting exposures that shape microbial colonisation, immune development, and ultimately child growth.

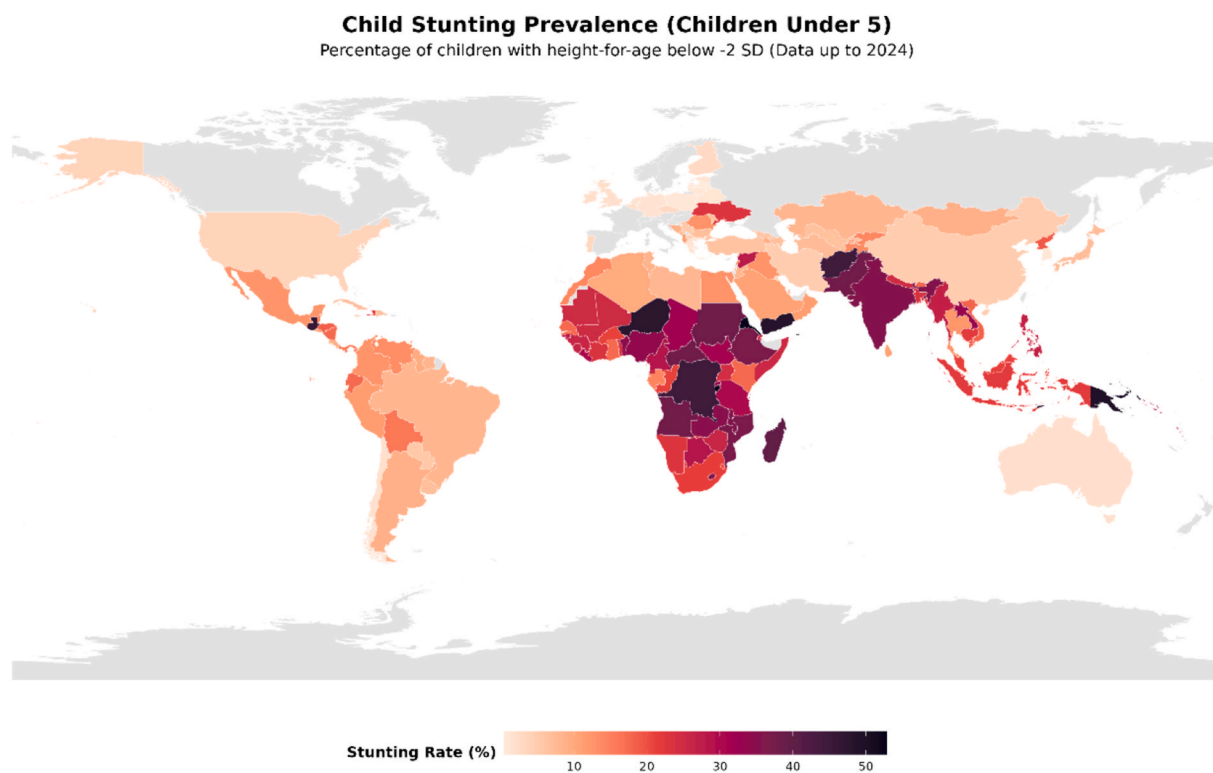


Fig. 2. Prevalence of stunting across the world. This map was created using data from the Joint Child Malnutrition Estimates [48]. The script used to generate this map can be found [here](https://github.com/DizzySpore/Gut-Microbiology-Literature-Review) (<https://github.com/DizzySpore/Gut-Microbiology-Literature-Review>).

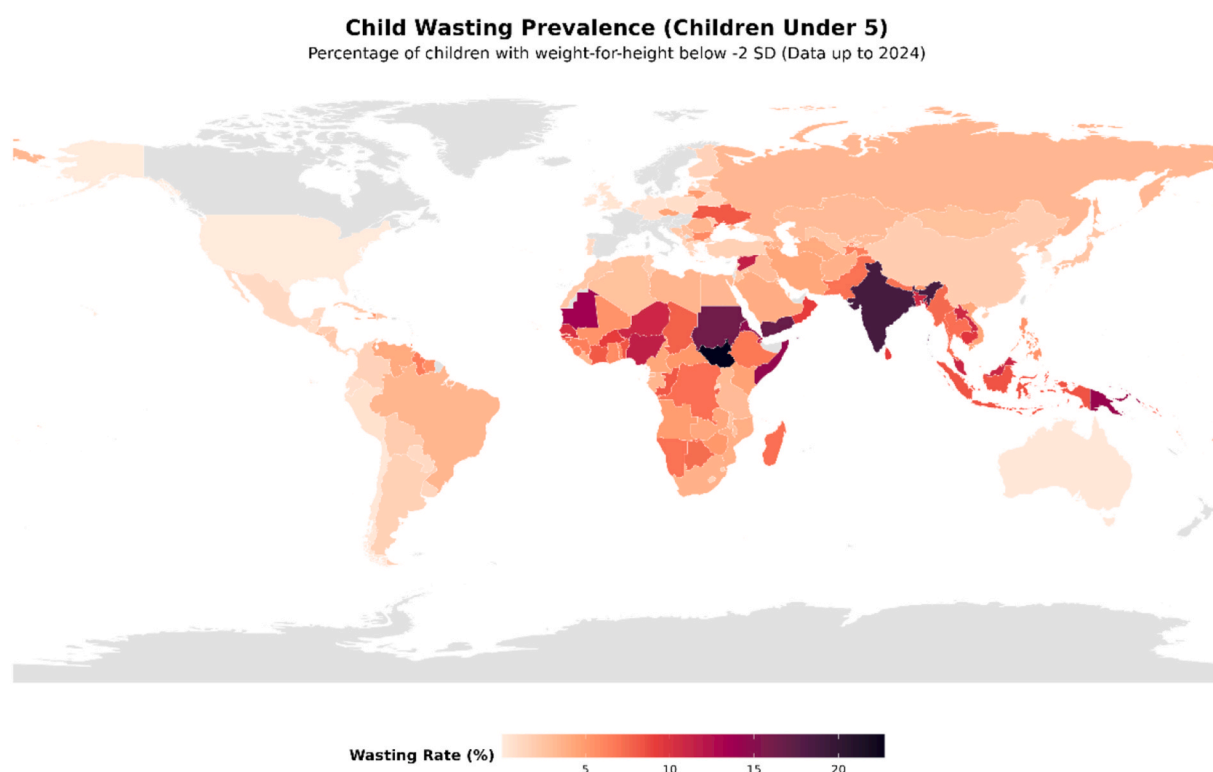


Fig. 3. Prevalence of wasting across the world. This map was created using data from the Joint Child Malnutrition Estimates [48]. The script used to generate this map can be found [here](https://github.com/DizzySpore/Gut-Microbiology-Literature-Review) (<https://github.com/DizzySpore/Gut-Microbiology-Literature-Review>).

3. Malnutrition, EED and the microbiome

3.1. Overview of malnutrition and its consequences

Undernutrition encompasses acute malnutrition (wasting), chronic malnutrition (stunting), and micronutrient deficiencies, each of which has distinct clinical manifestations and potential links to gut microbial composition and function [68]. In LMIC settings, these conditions frequently co-occur with high enteropathogen exposure, chronic inflammation, and EED, all of which can impair nutrient absorption and contribute to growth faltering. The following sections summarise the major forms of undernutrition and their consequences, as a background to understanding EED pathophysiology and its relationship with the gut microbiome [68].

Acute malnutrition, or wasting, is defined in children aged 6-59 months by a weight-for-height z-score (WHZ) < -2 or a mid-upper arm circumference (MUAC) < 12.5 cm⁶⁹. Severe acute malnutrition (SAM), defined by WHZ < -3 and MUAC < 11.5 cm, is a life threatening condition with mortality rates that may reach 30% in the presence of complications [69]. SAM compromises nutritional status through multiple mechanisms, including impaired intestinal barrier function, reduced Immunoglobulin A (IgA) secretion, thymic atrophy, and compromised cell-mediated immunity [70]. Increased mortality has been associated with a shift toward Th2-dominant inflammatory cytokine profiles [71]. Children with SAM also show characteristic microbiome alterations, including increased abundance of taxa within Pseudomonadota (formally Proteobacteria) such as *Escherichia*, *Klebsiella*, *Shigella*, alongside reduced representation of Bacteroidota, changes that may exacerbate malabsorption and inflammation [72].

Chronic malnutrition, or stunting, is defined by a height-for-age z-score (HAZ) < -2 , and reflects prolonged exposure to nutritional and environmental adversity [73,74]. Its causes are multifactorial and include recurrent undernutrition, frequent infections, low socioeconomic status, and suboptimal maternal and infant feeding practices. Unlike wasting, which reflects acute nutritional deficit, stunting is associated with impaired linear growth and long-term risks extending into later life. Stunted children exhibit distinct microbial patterns, including reduced *B. longum* and *Lactobacillus mucosae* and increased Enterobacteriaceae and *Desulfovibrio*. These shifts are associated with reduced SCFA production, impaired barrier integrity, and increased intestinal inflammation, thereby linking stunting to EED and growth faltering [75,76]. Chronic immune activation in this context is reflected by elevated biomarkers such as myeloperoxidase, α -1-antitrypsin and neopterin [77,78]. Persistent inflammation has also been associated with adverse neurodevelopmental outcomes and increased later life cardiometabolic risk [79,80].

Micronutrient deficiencies provide an additional route through which undernutrition may alter host-microbiome interactions. Deficiencies in nutrients such as selenium and zinc can impair immune function and constrain key enzymatic and metabolic pathways in both host and microbiota. Selenium deficiency may increase oxidative stress and weaken innate immunity, whereas zinc limitation can favour microbes with efficient metal acquisition systems, potentially contributing to microbiota perturbations [81,82]. Where multiple deficiencies co-occur, microbial and host responses may interact in ways that reduce responsiveness to nutritional rehabilitation [83].

3.2. Environmental enteric dysfunction(EED)

EED is defined as a chronic inflammatory disorder of the small intestine that is highly prevalent among children living in many LMICs and is strongly associated with malnutrition, immune dysregulation, and poor growth outcomes [84]. It is characterised by persistent intestinal inflammation, villous atrophy, barrier dysfunction and nutrient malabsorption [85,86]. As EED often presents sub-clinically, it may remain undetected until growth faltering or development impairment becomes

evident, by which point some consequences may be difficult to reverse [84].

Recent advances suggest that EED pathogenesis involves profound disruption of barrier function, epithelial renewal, and immunometabolic homeostasis [87]. Single-cell RNA sequencing studies of duodenal and jejunal biopsies have demonstrated altered epithelial differentiation, including reductions in enteroendocrine cell populations and abnormalities in Paneth cell maturation [88,89]. These disturbances may arise in part from chronic exposure to microbial products and endotoxins, which disrupt crypt-villus homeostasis and alter stem cell behaviour and lineage allocation [89,90].

Metabolic profiling has also identified biochemical signatures associated with EED [91]. Altered concentrations of phenolic compounds such as 4-cresol, phenylacetate, and urolithins point to a shift in protein fermentation and impaired host-microbe co-metabolism [92]. As such, metabolites can influence nuclear receptors involved in intestinal barrier regulation, they may contribute directly to EED pathophysiology [92]. At the transcriptomic level, maladaptive EED phenotypes have been associated with impaired inflammatory responses and disruption of metabolic pathways, including lipid metabolism and SCFA-associated processes, particularly in children with wasting [93].

Clinically, EED is characterised by growth faltering and other largely subclinical manifestations, including reduced nutrient absorption, villus blunting, lymphocytic infiltration, and microbial perturbations [85,86]. Overt symptoms are often non-specific and may include poor weight gain, stunting, or impaired cognitive development [85,86]. There is currently no universally accepted clinical standard for diagnosis, and most studies rely on combinations of functional tests, biomarkers, and where feasible, histology [85,86]. Common research tools include measures of intestinal permeability (e.g., Lactulose-to-Mannitol (L:M) ratios [85,86]), together with inflammatory markers. Emerging approaches include point-of-care measures of epithelial injury and integrated profiling of microbiome and metabolome features, although standardisation across settings remains limited [94]. Indeed, the marked heterogeneity of EED presentation and response suggests that stratified diagnostic and therapeutic approaches may ultimately be needed [91, 92].

EED is thought to arise from the interaction of nutritional deficiency, pathogen exposure, and environmental contamination. Diets low in essential amino acids (e.g., tryptophan), niacin, zinc and vitamin A have all been implicated, and disruption of zinc homeostasis in particular has been associated with increased intestinal permeability [95–97]. Oral-faecal contamination, environmental toxins, and repeated enteropathogen exposure further contribute to chronic inflammation and barrier disruption [98]. This in turn, increases energy expenditure, worsens malabsorption, and reinforces undernutrition [98]. Prolonged diarrhoea and persistent gut barrier dysfunction are both predictors of EED and subsequent malnutrition [99].

EED creates a vicious cycle with growth faltering and undernutrition [100]. Higher L:M ratios are negatively associated with linear growth velocity, while malabsorption and protein-loss enteropathy contribute to negative nitrogen balance [101–103]. Importantly, subclinical EED may precede overt growth faltering by 3-6 months, suggesting that intestinal dysfunction may be an early driver rather than simply a consequence of malnutrition [96]. Chronic intestinal inflammation also elevates inflammatory cytokines such as TNF- α can suppress growth hormone (GH) receptor expression and IL-6 can impair SOCS3 signalling leading to increased GH resistance in skeletal muscles and hepatocytes [104]. In parallel, inflammation-induced dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis may increase cortisol levels and promote protein catabolism [105]. Malabsorption of key micronutrients (A, D, zinc), further impairs epithelial repair and antimicrobial peptide production [100]. These mechanisms may help explain why some affected children remain deficient despite standard nutritional supplementation such as ready-to-use supplementary food (RUSF) or ready-to-use therapeutic foods (RUTF).

3.3. Effects of EED on the microbiome

EED and undernutrition are characterised by sustained inflammation, altered substrate availability, and impaired barrier function, all of which can reshape microbial community structure and reduce functional capacity [106]. These changes likely reflect both direct ecological selection within the gut and indirect effects of diet quality, infection burden, and antibiotic exposure. Chronic inflammation and nutrient inadequacy alter the gut metabolic environment in ways that favour opportunistic pathogens over beneficial microbes that support barrier function and metabolic production [106].

Reduced intake of complex carbohydrates can limit SCFA production, thereby weakening epithelial barrier integrity and altering immune homeostasis. Barrier dysfunction may also reduce expression of antimicrobial molecules such as Regenerating gene family protein III (RegIII) proteins, which normally help regulate Gram-positive bacteria at the mucosal surface [107,108]. Children with SAM show distinct microbial signatures and often reduced alpha diversity, findings that may be exacerbated by diarrhoea and impaired gut integrity [109,110]. Several studies have reported enrichment of potentially pathogenic bacteria, including *Shigella*, *Enterobacter*, *Streptococcus*, *Veillonella*, and *Escherichia*, while healthier microbiomes are more often characterised by SCFA-producing organisms such as *Roseburia* and *Butyrivibrio* [111]. Across cohorts, undernutrition and enteropathy have repeatedly been linked to relative enrichment of Pseudomonadota and depletion of taxa associated with SCFA production and HMO utilisation, although the exact patterns vary by population and analytical approach [72].

Particularly important is the depletion of beneficial *Bifidobacterium* species such as *B. longum* subsp. *longum*, *B. longum* subsp. *infantis*, and *B. breve*, which are central to early-life HMO metabolism and are associated with SCFA production and immune modulation [112,113]. Loss of these taxa may reduce efficient milk utilisation and further weaken host-microbe interactions [114]. At the same time, expansion of opportunistic pathogens such as Enterobacteriaceae or Clostridiales may generate toxic metabolic byproducts, promote inflammation, and contribute to unfavourable SCFA profiles, thereby increasing susceptibility to infection and further microbiome disruption [115,116].

These microbiome perturbations may contribute directly to growth faltering through impaired barrier integrity, altered nutrient absorption, and dysregulated host growth signalling. Reduced abundance of SCFA-producing bacteria can weaken epithelial tight junctions, while secondary disaccharidase deficiency may develop in the context of chronic gut inflammation, increasing osmotic load, fluid loss, and bacterial fermentation [117–119]. Protein-losing enteropathy associated with gut barrier dysfunction can markedly increase gastrointestinal albumin loss and reduce circulating albumin concentrations [120]. Fat malabsorption may also be aggravated by reduced bile acid availability, contributing to deficiencies in fat-soluble vitamins such as A, D, E, and K.

Taken together, EED provides a mechanistic link between LMIC environmental exposures, impaired growth, and heightened susceptibility to infection. Recurrent enteropathogen exposure and chronic intestinal inflammation reduce absorptive capacity and increase permeability, creating an inflamed, nutrient-poor intestinal environment that favours opportunistic taxa while suppressing taxa that support barrier integrity and metabolite production. This perturbed state may reduce colonisation resistance and impair immune education, increasing the likelihood of subsequent infections. Each infectious episode may further reduce appetite, limit nutrient availability, and increase inflammatory signalling, thereby reinforcing both EED physiology and microbiome immaturity. Framing EED as a central “hinge” in this cycle helps explain why nutrition rehabilitation alone may be insufficient when enteropathy and inflammation persist, and why microbiome-directed strategies are increasingly being pursued.

4. Infection and the microbiome in LMIC infants

4.1. Common infectious diseases affecting infants in LMICs

Infection risk in early life is shaped by complex interactions between nutritional status, immune development, environmental exposure, and the gut microbiome [59]. These risks are amplified in many LMIC settings, where infants are more likely to experience undernutrition, poor sanitation and hygiene, high enteropathogen exposure, and limited access to timely healthcare [121]. Together, these factors increase susceptibility to infection while also disrupting microbiome maturation and intestinal barrier function.

LMICs bear a disproportionate burden of infectious diseases, with infants being particularly vulnerable. Bacterial infections are a major contributor to morbidity and mortality, followed by viral and parasitic infections [122–125]. Neonatal sepsis remains one of the most serious infectious threats and accounts for up to a quarter of all neonatal deaths [122–125]. In many LMIC settings, neonatal sepsis is predominantly caused by Gram-negative organisms, with *Escherichia* and *Klebsiella* species among the most frequently reported pathogens [126]. Risk is increased by poor hygiene, maternal infections, limited vaccination coverage, high rates of preterm births, and poor maternal or infant nutritional status [121].

Diarrhoeal illness is also common in early life in LMIC settings, although estimates vary by region, surveillance method, season, and study design. Respiratory infections are similarly frequent and remain an important cause of infant morbidity and mortality. For example one cross-sectional study from Bangladesh, diarrheal disease affected up to 40.8% of children, while respiratory disease had a prevalence of 35.7% [59]. Nutritional status is strongly associated with risk of diarrheal disease and is also linked to respiratory infection risk [59,127]. Among the most common diarrhoeal pathogens, rotavirus and by *Shigella* spp. are reported as the common contributors to disease burden, although pathogen profiles vary substantially across settings and age groups (Fig. 4).

Respiratory diseases, including pneumonia, are less frequent than diarrhoeal illness in some cohorts but carry a high risk of death, particularly in sub-Saharan Africa and South Asia [128,129]. Undernutrition and a disrupted microbiome can impair immune function, weaken barrier defences and reduce colonisation resistance, thereby increasing susceptibility to both enteric and systemic infection. These relationships are bidirectional, as infection can further disrupt the microbiome, worsen nutrient loss, and reinforce inflammatory pathways linked to EED and growth faltering.

4.2. Bidirectional interaction of infection and the microbiome

The gut microbiome contributes to colonisation resistance by occupying ecological niches, limiting nutrient availability for invading pathogens, producing inhibitory metabolites, and strengthening epithelial barrier function [130,131]. In early life, breastmilk supports taxa such as *Bifidobacterium* through the provision of HMOs. Taxa like *Bifidobacterium* produce microbial fermentation products, including SCFAs, reinforce mucosal integrity and may reduce luminal pH, thereby limiting the growth of acid-sensitive enteric pathogens and, at sufficient concentrations, disrupting bacterial metabolism [38,132–139].

Commensal microbes also contribute to immune maturation. *Bifidobacterium* and other early-life commensals can support development of regulatory T cells, while the microbiome more broadly promotes maturation of gut-associated lymphoid tissue (GALT) [140,141]. Regulatory T cells are central to immune tolerance, helping distinguish between commensal bacteria and pathogenic threats [142]. Disruption of these early microbial signals may therefore impair immune education and alter inflammatory responses.

Perturbations to microbiome development due to infection, undernutrition, antibiotic exposure, or other environmental pressures have



Fig. 4. Heatmap of Disability-Adjusted Life Years (DALYs) attributable to diarrhoeal disease by pathogen. This figure was based on Institute of Health Metrics and Evaluation's (IHME's) 2021 edition of global burden of disease estimates for pathogens and AMR [128] (Accessed: 09.02.2026). The script used to generate this map can be found [here](https://github.com/DizzySpore/Gut-Microbiology-Literature-Review) (<https://github.com/DizzySpore/Gut-Microbiology-Literature-Review>).

been associated with increased susceptibility to disturbances later in life [143–145]. These perturbations may delay microbiome maturation, weaken physical barriers such as the mucin layer [143,146], and reduce colonisation resistance. They may also contribute to poorly regulated immune responses and persistent low-grade inflammation, even when pathogen exposure is intermittent [143,146]. In turn, inflammation and infection can reduce appetite, increase nutrient losses, impair absorption, and further compromise immune function, thereby reinforcing EED and delayed microbiome maturation.

Taken together, the evidence supports a self-reinforcing cycle in which infection perturbs microbiome assembly and function, while microbiota disturbances and impaired immune maturation increase vulnerability to further infection. This has important translational implications. Interventions that improve growth without restoring microbiome maturation, reducing inflammation, or lowering enteropathogen exposure may produce incomplete or transient benefits. The following section therefore considers current intervention strategies, including nutrition-based rehabilitation and emerging microbiome-directed approaches, in relation to the mechanisms outlined below.

5. Current translational research and microbiome-directed interventions

Translational strategies to address undernutrition have historically focused on caloric and micronutrient repletion, particularly through ready-to-use therapeutic and supplementary foods. However, growing mechanistic evidence linking microbiome immaturity, EED, and impaired growth has motivated approaches that aim not only to restore

nutritional status, but also promote microbial community recovery and function. Below, we summarise current evidence across nutrition-based rehabilitation, biotic supplementation, and microbiota-directed complementary foods, while considering implementation factors that may determine real-world effectiveness in LMIC settings.

RUTF/RUSF remain central to management of acute malnutrition. These interventions provide energy dense, bioavailable mixtures of lipids, amino acids, and micronutrients that can reduce mortality, prevent muscle wasting, and support metabolic recovery in children with wasting and SAM [147–149]. Their relatively small dosage volume may also help avoid displacement of other important nutrient sources such as breastmilk [148]. However, systematic reviews highlight uncertainty around optimal dosing and duration, and effectiveness may vary according to comorbidity, enteropathy, infection burden, and local context. Importantly, RUTF/RUSF have limited effects on linear growth, and do not resolve EED, indeed in some cases, persistent enteropathy and inflammation may limit response to nutritional rehabilitation [150].

Evidence for probiotics and synbiotics in undernourished children remains mixed. Randomised trials and meta-analyses have reported variable effects on growth outcomes, likely reflecting differences in strain selection, dose, baseline microbiome composition, concurrent infection burden, and environmental exposures [151]. For example, the SYNERGIE trial in Bangladesh found that supplementation with *B. longum* subsp. *infantis* EVC001 significantly increased WAZ and MUAC compared with placebo [152]. However, the subsequent CONSTELLATION study in Pakistan, which assessed different strains, did not detect significant improvements in weight gain or anthropometric outcomes [153]. These findings suggest that probiotic efficacy is unlikely to be

generic and may depend on careful matching of strain, host context, diet, and ecological niche availability.

More recent research has therefore shifted towards microbiota-directed complementary foods (MDCF), which are designed to repair microbiome immaturity by providing substrates that selectively promote growth of beneficial taxa [154]. Studies in Bangladesh showed that childhood malnutrition is associated with “taxonomic immaturity”, whereby the gut microbiota of a malnourished child resembles that of a younger child rather than an age-matched healthy peer [56]. Early MDCF approaches produced only transient microbiome improvements, with relapse after treatment cessation, suggesting that perturbation was not simply a consequence of caloric deficiency but also reflected the absence of specific microbial growth substrates [56,155,156].

This led to the development of MDCF-2, a formulation designed to provide substrates that support taxa associated with a healthy microbiome maturation [155,156]. In a RCT in Bangladesh, MDCF-2 was compared with standard RUSF in children with moderate acute malnutrition while both groups improved over three months, children receiving MDCF-2 showed a greater rate of improvement in weight-for-age and weight-for-length Z-scores, despite MDCF-2 having a lower caloric density than RUSF [154]. Subsequent analysis suggested that the presence of *Segatella copri* may enhance response to MDCF treatment, contributing to greater weight gain for a given caloric intake [157]. These findings support the idea that provision of appropriate microbial substrates can promote expansion of beneficial taxa, enhance microbiome maturation, which improve growth outcomes beyond what would be expected by calories alone.

Together, these studies indicate that microbiome-directed interventions may offer an important complement to conventional nutritional rehabilitation. However, their effectiveness is likely to depend on baseline microbiome state, dietary context, infection burden, and

environmental exposures. Future interventions may therefore need to combine nutritional support with strategies that reduce enteropathogen pressure, improve gut barrier recovery, and promote durable microbiome maturation.

6. Key knowledge gaps and future research directions

Several evidence gaps limit generalisable understanding of early-life microbiome development and its relationship with growth in LMIC settings. These include (i) geographic under-representation and limited longitudinal sampling, (ii) insufficient integration of functional read-outs, including metabolomics, proteomics, and immunophenotyping, with microbial community profiles, (iii) incomplete reference catalogues for locally prevalent strains and non-bacterial members of the microbiome, and (iv) limited understanding of how context-specific exposures modify responses to nutritional and microbiome-directed intervention response. Although broad patterns of early-life microbiome development have been described, the resolution of available data remains substantially lower in LMICs early life than in HICs, particularly for longitudinal cohorts [158,159]. This imbalance is reflected in the global distribution of human gut microbiome studies, the majority of which originate from HIC populations (Fig. 5).

Microbiome heterogeneity may be greater in many LMIC settings than in HICs, reflecting wider variation in diet, environmental exposures, sanitation, infection burden and healthcare access [162–164]. As a result, normative developmental trajectories of early-life microbiome maturation remains poorly defined across many regions [165–167], and the extent of geographic variation is still incompletely characterised [165,166]. Establishing robust reference trajectories early life would provide a baseline against which microbiome perturbations associated with malnutrition, antibiotic exposure, infection, and EED could be

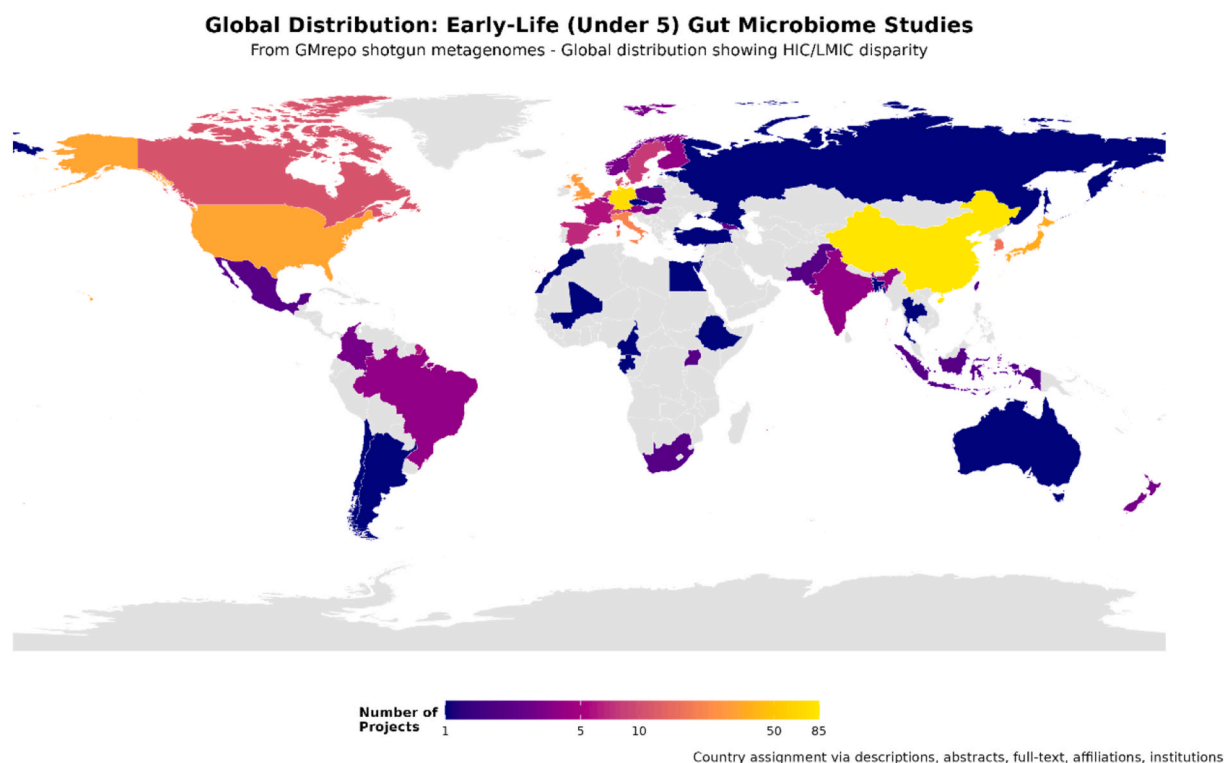


Fig. 5. Distribution of gut microbiome studies across the world. This map was created by assigning country of origin to projects listed in the Gut Microbiome Repository (GMrepo) [160] (Accessed: 16.02.2026). Country of origin and early-life status were assigned using a custom Python script by parsing entries from GMrepo based on: 1. The population descriptions in GMrepo's database metadata, 2. The project descriptions listed in GMrepo's database metadata, 3. Abstracts of associated papers accessed through dois listed in GMrepo's database metadata, 4. Methods sections of associated papers, 5. Submitting organisations listed on ENA [161]. Projects assigned to multiple countries were counted once for each country assigned. The script used to generate this map can be found [here](https://github.com/DizzySpore/Gut-Microbiology-Literature-Review) (<https://github.com/DizzySpore/Gut-Microbiology-Literature-Review>).

quantified [167]. With dense longitudinal sampling and well-annotated exposure data, deviations from these ‘reference’ patterns may help identify dominant drivers of disruption within and between populations [167].

A further gap concerns the mechanisms through which specific taxa influence immune and nutritional outcomes. For example, although *S. copri* has been associated with enhanced response to MDCF treatment, the mechanisms underlying its effect on early-life immune development remains poorly understood. Recent work has shown *S. copri* outer-membrane vesicles can induce pro-inflammatory responses in macrophages, but whether these findings translate to infant intestinal immunity remains unknown [168]. In contrast, immunomodulatory mechanisms have been described in greater detail for other taxa such as *Bacteroides fragilis* through polysaccharide A and several *Bifidobacterium*-associated pathways, highlighting the need for comparable mechanistic studies of *S. copri* and other candidate taxa [169,170].

Non-bacterial members of the microbiome are also underexplored in early life, particularly in LMIC settings. Archaea and methane metabolism may influence gut ecology and nutrition-relevant physiology, yet their contribution to early-life microbiome development remains poorly understood [171–173]. Studying archaea is technically challenging because many are strict anaerobes, grow slowly, and are present at much lower abundance than bacteria, making them difficult to culture and isolate [172,174]. Nevertheless, despite their low abundance, archaea may play important roles in hydrogen metabolism, fermentation efficiency, and wider microbial network function [175].

Bacteriophages are another important yet understudied crucial component of the gut microbiome, particularly in LMIC contexts [176, 177]. Phages play a major role in shaping bacterial population dynamics and act as key mediators of horizontal gene transfer [178,179]. Through both lytic infection abundances and lysogenic integration, bacteriophages can alter bacterial abundance, influence community composition, and drive strain-level turnover [178,179]. A deeper understanding of early life phageome therefore represents an important knowledge gap in microbiome research, particularly in underrepresented populations and geographical regions.

Addressing these gaps will require expanded longitudinal multi-omic datasets, improved reference catalogues for locally prevalent strains, and greater recovery and sequencing of isolates from LMIC cohorts. Integrating metagenomics with metabolomics, immune profiling, pathogen surveillance, dietary assessment, and environmental exposure data will be essential for distinguishing correlation from mechanism. In parallel, targeted profiling of the archaeome and other non-bacterial community members may clarify how microbial-associated pathways differ across settings and contribute to nutrition-relevant physiology during early development. Such efforts will be critical for designing diagnostics and interventions that are generalisable, context-sensitive, and scalable.

7. Implications for public health policy and practices

Therapeutic foods and microbiome-relevant adjuncts that promote microbiome maturation alongside nutritional recovery could offer an additional route to reducing the short- and long-term consequences of early-life undernutrition [180]. These strategies may show clearest near-term benefits in wasting and SAM, where clinical trajectories can be modified over relatively short time scales [157]. Effects on stunting are likely to be more context-dependent given the chronic nature of linear growth faltering and need for earlier identification, sustained nutritional support, and reduction of enteropathogen, and inflammatory burden [181,182].

Implementation factors will strongly shape real-world impact. Shelf stability, supply chains, cost, acceptability, regulatory oversight, and local production capacity will influence feasibility at scale [183]. Local production may improve access and affordability but can introduce variability in formulation, composition, and quality if standardisation is

limited. Conversely centralised production may support quality control but can create barriers related to distribution, procurement and equity [184]. These considerations highlight that translational success will depend not only on biological efficacy, but also on delivery systems that are affordable, culturally acceptable, and robust across diverse LMIC contexts.

More broadly, microbiome-directed strategies should not be viewed as replacements for established public health interventions, but as potential complements. Their impact is likely to be greatest when integrated with breastfeeding support, appropriate complementary feeding, improved WASH infrastructure, infection prevention, antimicrobial stewardship, and early identification of growth faltering and EED. A combined approach that addresses both microbial recovery and the environmental pressures that drive perturbation may be necessary to achieve sustained improvements in growth and immune development.

8. Conclusions

Early-life undernutrition in LMIC settings commonly occurs alongside high enteropathogen exposure, repeated infection, and inflammatory gut pathology, including EED. Together, these pressures are associated with delayed or perturbed microbiome maturation. Across studies, wasting, stunting, and micronutrient deficiencies are linked to microbial compositional and functional shifts that may weaken barrier integrity, reduce colonisation resistance, impair nutrient utilisation, and alter immune development. Infection can further disrupt microbiome assembly, both directly and indirectly through antibiotic exposure, while inflammation and malabsorption may limit effectiveness of nutrition-only rehabilitation in some contexts.

Microbiome-directed interventions, including MDCFs and selected biotic approaches, are being evaluated as strategies to support microbiome maturation alongside nutritional recovery and improved growth. However, current evidence remains heterogeneous and strongly context-dependent. Key priorities include improving geographic representation, expanding longitudinal multi-omic cohorts, and establishing functional benchmarks of ‘healthy’ maturation across diverse LMIC settings. From an implementation perspective, shelf stability, supply chains, cost, acceptability, and equity will be critical determinants of real-world impact. As these interventions move towards scale, it will also be important to consider potential unintended consequences, including whether efforts to promote ‘healthy’ maturation could inadvertently homogenise microbiomes across ecologically and culturally diverse early life contexts.

CRedit authorship contribution statement

Leon Mijić: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis. **Mishal Shaheen:** Writing – original draft. **Angeziwa Chunga:** Writing – review & editing. **Raymond Kiu:** Writing – original draft. **Lindsay J. Hall:** Writing – original draft, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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