REVIEW

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Gut microbiota-targeted nutritional interventions for growth recovery in children with acute malnutrition: A systematic review

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ABSTRACT

Background: Acute malnutrition in children is a clinical condition characterized by rapid weight loss, wasting muscle mass, and impaired nutrient absorption. This systematic review aims to evaluate the effectiveness of gut microbiota on growth recovery in children with acute malnutrition.

Methods: This systematic review was developed following the PRISMA 2020 guidelines. A literature search was conducted in three electronic databases, namely PubMed, ScienceDirect, and Cochrane. Included studies were randomized clinical trials and controlled trials evaluating gut microbiota-based nutritional interventions in children with acute malnutrition. Data was analyzed qualitatively.

Result: Fourteen studies met the inclusion criteria, encompassing a total of 3,833 subjects (please verify against **Table 1**) from various low- and middle-income countries. The interventions evaluated included microbiota-directed complementary foods (MDCF), probiotics, prebiotics, synbiotics, and locally sourced therapeutic formulas. MDCF was associated with the most consistent improvements in Weight-for-Length Z-score (WLZ), Weight-for-Age Z-score (WAZ), and Mid-Upper Arm Circumference (MUAC), and growth-related biological profiles across included studies. Certain probiotic strains, particularly Bifidobacterium infantis EVC001, provided significant ponderal improvements in some populations, although consistency across studies was limited. Prebiotics and locally sourced formulas demonstrated potential benefits on certain outcomes, but results varied

Conclusion: Nutritional interventions targeting the gut microbiota, particularly MDCF, have the potential to support growth recovery in children with acute malnutrition. Their effectiveness depends heavily on the type of intervention, its composition, the child's age, the malnutrition category, and the duration of administration.

Keywords: Acute malnutrition, gut microbiota, growth recovery, nutritional intervention, systematic review.
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INTRODUCTION

Acute malnutrition in children is a clinical condition characterized by rapid weight loss, wasting of muscle mass, and impaired nutrient absorption. It is classified as moderate acute malnutrition (MAM) with a weight-for-length Z-score (WLZ) between -2 and -3 SD, and severe acute malnutrition (SAM) if the WLZ is below -3 SD or the mid-upper arm circumference is less than 115 mm. This condition is not solely the result of inadequate food intake, but is also influenced by recurrent infections, impaired intestinal function, and immune system dysregulation, which are interconnected in a cycle that is difficult to break.[1] Undernutrition broadly (including acute and chronic forms) contributes to approximately 45% of all deaths in children under five years globally; the specific attributable fraction for acute malnutrition alone may be lower, with hospitalized mortality rates from SAM still ranging from 10% to 40% in low- and middle-income countries.[2,3] The scale of this problem highlights that current therapeutic approaches are unable to adequately address all dimensions of the pathophysiology of acute malnutrition in children.

Current standard management of acute malnutrition relies on the provision of ready-to-use therapeutic food (RUTF) and ready-to-use supplementary food (RUSF), designed to meet the energy and macronutrient needs of malnourished children. Although these interventions have been shown to accelerate weight gain in the early phase of recovery, a high proportion of children relapse post-treatment, and complete anthropometric recovery is often not achieved within the intervention period.[4] Research findings over the past decade have consistently demonstrated gut microbiota immaturity, a condition in which the composition and diversity of the gut bacterial community do not develop according to the child's chronological age.[5] This dysbiosis is characterized by an increased proportion of Proteobacteria, a decrease in Bacteroidetes, and reduced production of short-chain fatty acids, which play a role in intestinal epithelial integrity and immune programming.[1] Of further

concern is that this microbiota immaturity does not fully resolve after conventional nutritional interventions are discontinued, raising the question of whether sustained growth recovery can be achieved without first specifically improving the gut microbial ecosystem.[6,7] Numerous clinical trials have explored the role of probiotics, prebiotics, and synbiotics as strategies to modulate the gut microbiota in malnourished children, but results have shown substantial inconsistencies in both the type of intervention, the strains of microorganisms used, the duration of administration, and the growth outcomes assessed.[8,9]

The inconsistency in findings across studies is largely due to population heterogeneity, variations in the severity of malnutrition studied, and differences in the definitions of recovery outcomes used. Studies specifically comparing the effectiveness of various microbiota-based intervention modalities, ranging from microbiota-directed complementary food (MDCF) and synbiotics to their combinations, in children with confirmed acute malnutrition have not been systematically summarized in a single integrated review. Critically, no previous review has provided an integrated synthesis that simultaneously stratifies interventions by their microbiota-targeting mechanism, distinguishing microbiota-directed complementary foods from probiotic, prebiotic, and synbiotic approaches, while restricting the evidence base to children with confirmed acute malnutrition and evaluating outcomes across both anthropometric growth recovery and microbiota-related biological profiles. A novel framework that integrates an understanding of gut microbiota modulation mechanisms with anthropometric growth recovery outcomes is urgently needed to provide a more solid evidence base for child nutrition management policies. This systematic review aims to comprehensively evaluate the effectiveness of nutritional interventions targeting the gut microbiota on growth recovery in children with acute malnutrition and to identify intervention characteristics most associated with optimal anthropometric outcomes.

METHODS

This systematic review was prepared based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[10] Registration through PROSPERO is not available.

Literature Search Strategy

A systematic literature search was conducted in three electronic databases: PubMed, ScienceDirect, and Cochrane Library. No date restrictions were applied to the search, and no language restrictions were imposed. The search was conducted using a combination of keywords structured according to the components of population, intervention, comparator, and outcome, employing Boolean operators AND and OR to broaden and narrow results as needed.

In PubMed, the following search string was applied across all fields: ("gut microbiota" OR "gut microbiome" OR "intestinal microbiota" OR "intestinal microbiome" OR "microbiome" OR "microbiota") AND ("acute malnutrition" OR "severe acute malnutrition" OR "moderate acute malnutrition" OR "SAM" OR "MAM" OR "wasting" OR "undernutrition") AND ("children" OR "infant" OR "pediatric" OR "paediatric") AND ("probiotic" OR "prebiotic" OR "synbiotic" OR "microbiota-directed complementary food" OR "MDCF" OR "microbiome-directed food" OR "nutritional intervention" OR "therapeutic food") AND ("growth" OR "weight gain" OR "nutritional recovery" OR "anthropometric" OR "WLZ" OR "WHZ" OR "WAZ" OR "LAZ" OR "HAZ" OR "MUAC"). The search was further filtered to include only randomized controlled trials and clinical trials using the built-in publication type filter available in PubMed.

In ScienceDirect, the search was conducted using the following string in the Title, Abstract, and Keywords fields: ("gut microbiota" OR "gut microbiome" OR "intestinal microbiota") AND ("acute malnutrition" OR "severe acute malnutrition" OR "moderate acute malnutrition" OR "wasting") AND ("children" OR "infant" OR "pediatric") AND ("probiotic" OR "prebiotic" OR "synbiotic" OR "MDCF" OR "microbiota-directed" OR "therapeutic food") AND ("growth" OR "weight gain" OR "anthropometric" OR "WLZ" OR "WAZ" OR "MUAC"). Results were filtered to include only research articles and review articles, with the article type subsequently refined to include only original research during full-text screening.

In the Cochrane Library, the search was conducted in the Cochrane Central Register of Controlled Trials (CENTRAL) using the following string: ("gut microbiota" OR "gut microbiome" OR "intestinal microbiota" OR "microbiome") AND ("acute malnutrition" OR "severe acute malnutrition" OR "moderate acute malnutrition" OR "wasting" OR "SAM" OR "MAM") AND ("children" OR "infant" OR "pediatric" OR "paediatric") AND ("probiotic" OR "prebiotic" OR "synbiotic" OR "microbiota-directed complementary food" OR "MDCF" OR "therapeutic food" OR "nutritional intervention") AND ("growth" OR "weight gain" OR "anthropometric" OR "WLZ" OR "WAZ" OR "MUAC" OR "nutritional recovery"). No additional filters were applied within the Cochrane interface beyond the inherent restriction of CENTRAL to controlled trials.

The search results from each database were exported to a reference management tool to identify and remove duplicates. The remaining records proceeded to title and abstract screening, followed by full-text assessment against the pre-established eligibility criteria.

Eligibility Criteria

Inclusion criteria included studies in children within the pediatric age range, predominantly aged 0 to 59 months, or as defined by the investigators in each study, with moderate acute malnutrition, severe acute malnutrition, uncomplicated acute malnutrition (SAM), hospitalized SAM, MAM, or the recovery phase after acute malnutrition. Interventions included microbiota-directed complementary foods, microbiome-directed therapeutic foods, probiotics, prebiotics, synbiotics, or nutritional formulas that explicitly target the gut microbiota or gastrointestinal ecology. Acceptable comparators included placebo, standard care, RUTF, RUSF, F-75, F-100, control formulas, or other

standard nutritional interventions that do not specifically target the gut microbiota. Primary outcomes included weight gain, nutritional recovery, WLZ/WHZ, WAZ, LAZ/HAZ, MUAC, and time to recovery, while secondary outcomes included microbiota maturation, biomarkers of environmental enteric dysfunction or intestinal inflammation, diarrhea, pneumonia, hospitalization, mortality, relapse, and adverse events. Studies excluded included studies in adults, healthy populations without malnutrition data, studies without a clear comparison group, interventions without a microbiota-targeting component, observational studies without interventions, case reports, case series, narrative reviews, systematic reviews, meta-analyses, editorials, protocols without results, conference abstracts without complete data, and animal or in vitro studies without pediatric clinical data. Secondary analyses from the same parent trial population were included for mechanistic synthesis and were not counted as independent studies in the narrative synthesis.

Table 1. PICOS Framework.

Component	Eligibility Criteria
Population (P)	Children within the pediatric age range, predominantly aged 0 to 59 months, diagnosed with: • Moderate acute malnutrition (MAM): WLZ between −2 and −3 SD • Severe acute malnutrition (SAM): WLZ below −3 SD or MUAC <115 mm • Uncomplicated SAM, hospitalized SAM, or post-SAM recovery phase • Age criteria as defined by the investigators in each included study
Intervention (I)	Nutritional interventions explicitly targeting the gut microbiota or gastrointestinal ecology, including: • Microbiota-directed complementary foods (MDCF) • Microbiome-directed therapeutic foods • Probiotics, prebiotics, and synbiotics • Locally sourced nutritional formulas with demonstrated or intended microbiota-modulating properties
Comparator (C)	Placebo, standard care, RUTF, RUSF, WHO therapeutic formulas (F-75, F-100), fortified blended flour, or other standard nutritional interventions **not** specifically targeting the gut microbiota
Outcomes (O)	**Primary:** weight gain, nutritional recovery, WLZ/WHZ, WAZ, LAZ/HAZ, MUAC, and time to recovery **Secondary:** gut microbiota maturation, biomarkers of environmental enteric dysfunction or intestinal inflammation, diarrhea, pneumonia, hospitalization, mortality, relapse, and adverse events
Study Design (S)	**Eligible:** randomized controlled trials (RCTs) and controlled clinical trials **Note:** Secondary analyses from parent trial populations were included for mechanistic synthesis but were not counted as independent studies in the narrative synthesis **Excluded:** observational studies, case reports, case series, narrative reviews, systematic reviews, meta-analyses, editorials, conference abstracts without complete data, protocols without results, and animal or in vitro studies

Study Selection and Data Extraction

Study selection was conducted in two stages: title and abstract screening, followed by full-text assessment of articles potentially meeting the inclusion criteria. Two reviewers conducted the selection independently, and any discrepancies were resolved through discussion or by a third reviewer if consensus could not be reached. The selection process was documented in a PRISMA 2020 flowchart. Data extraction was performed using a standardized form that included author name, year of publication, country, study location, study design, number of subjects, population characteristics, malnutrition category, age range, type of intervention, intervention composition and dose, duration of administration, duration of follow-up, type of comparator, standard care or co-intervention, primary outcome, secondary outcome, main outcome, effect size, confidence interval, and p-value, if available.

Risk of Bias Assessment

The risk of bias for each randomized clinical trial was assessed using the Cochrane Risk of Bias 2 (RoB 2) criteria. The assessment was conducted across five domains: the randomization process, deviations from the intended intervention, missing outcome data, outcome measurements, and selection of reported outcomes. Each domain was classified as low risk of bias, some concerns, or high risk of bias according to the RoB 2 algorithm. Assessments were conducted independently by two reviewers, and discrepancies were resolved through discussion until consensus was reached. The final results of the risk of bias assessment are presented in the form of summary tables, traffic light plots, and summary diagrams of the proportion of risk of bias in each domain.

Data Synthesis

Data synthesis was conducted narratively. Studies meeting the inclusion criteria were grouped by intervention type: microbiota-directed complementary foods, microbiome-directed therapeutic foods, probiotics, prebiotics, synbiotics, or other nutritional formulas targeting the gut microbiota. Synthesis was also performed based on malnutrition category, comparator type, intervention duration, follow-up duration, and reported outcomes. Growth outcomes were analyzed through weight change, nutritional recovery, WLZ/WHZ, WAZ, LAZ/HAZ, MUAC, and time to recovery. Microbiota outcomes and intestinal biomarkers were analyzed to assess changes in microbiota composition or maturation, biomarkers of environmental enteric dysfunction,

and intestinal inflammation. Clinical outcomes, including diarrhea, pneumonia, hospitalizations, mortality, relapse, and adverse events, were synthesized to assess the clinical benefit and safety of the intervention. The results of each study are presented in a table of study characteristics and a structured narrative comparing the direction of effect, consistency of findings, and methodological limitations across studies.

RESULTS

Literature Search

The study selection process was conducted using the PRISMA flowchart. The initial search of three databases yielded 868 articles, consisting of 375 articles from PubMed, 439 articles from ScienceDirect, and 54 articles from Cochrane. Fifty-nine duplicate articles were removed before the screening process, leaving 809 articles to proceed to the title and abstract screening stage. At this stage, 786 articles were excluded because they did not meet the focus and eligibility criteria of the systematic review. A total of 23 articles were then searched in full text, and all articles were retrieved. These 23 articles were then thoroughly assessed for eligibility. Nine articles were excluded due to irrelevant data, while no articles were excluded due to incomplete data. At the end of the selection process, 14 studies with 14 published reports were included in this systematic review.

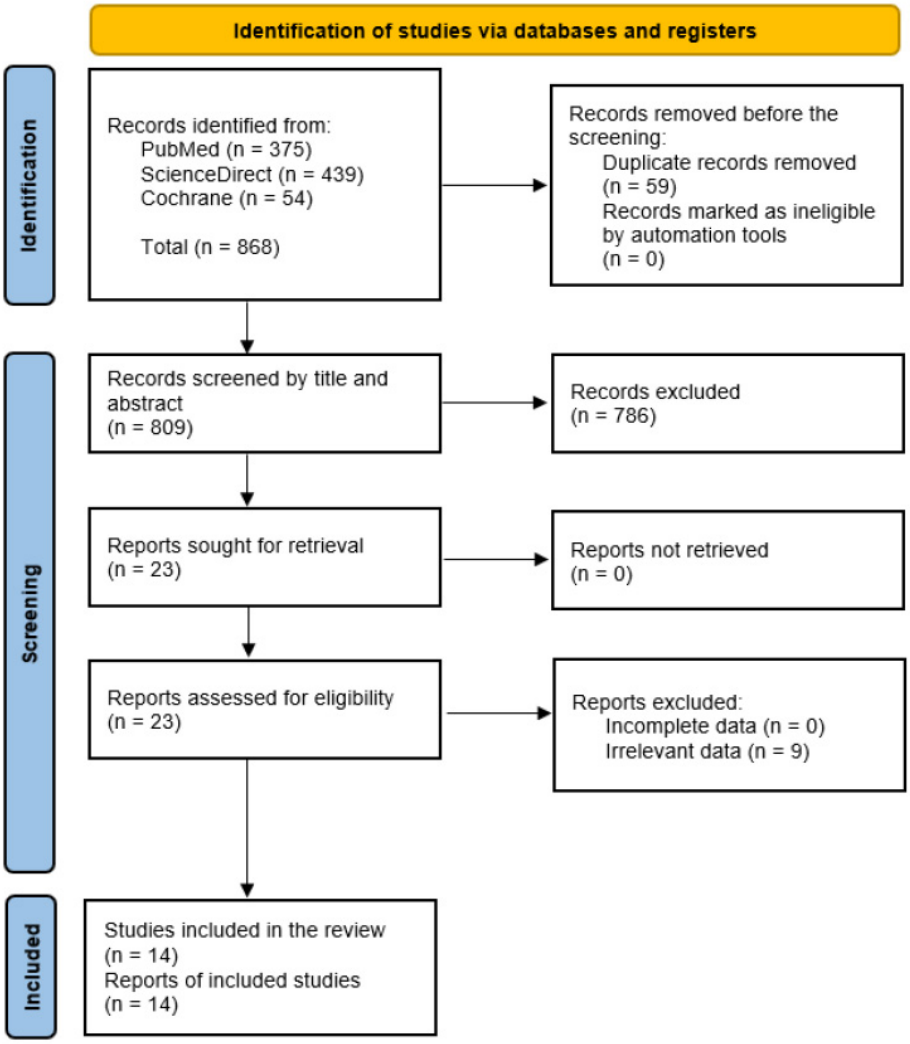


Figure 1. PRISMA Flowchart.

Study Characteristics

Based on Table 2, this systematic review includes 14 studies published between 2009 and 2026.[4,7,19–22,11–18] Most studies used a randomized clinical trial design, while some studies used an open-label randomized trial design, a phase II randomized controlled trial, a pragmatic randomized trial, and a follow-up analysis of previous clinical trials.[13,18–21] Studies originate from a variety of low- and middle-income countries, with a predominance of research from Bangladesh and Uganda, followed by Malawi, the Democratic Republic of the Congo, Pakistan, India, Indonesia, as well as multicenter studies in Niger, the Central African Republic, Senegal, and Madagascar. Sample sizes varied between 58 and 881 subjects, resulting in wide variation in population coverage and data strength between studies.[13,20]

The included study populations included children with moderate acute malnutrition, severe acute malnutrition, uncomplicated severe acute malnutrition, hospitalized severe malnutrition, and children in the recovery phase after severe acute malnutrition.[4,7,11–14,16,17,21] The age range of study subjects was also quite diverse, ranging from infants aged 2 to 6 months to children aged 168 months in the 2009 Kerac study.[7,11] Most studies focused on children under 5 years of age, in line with the primary target of acute malnutrition management programs in children.[12,15,16,22] The Chen, Barratt, Hartman, and Mostafa study specifically examined children aged 12 to 18 months, providing a more homogeneous group of data for assessing the effects of microbiota-based interventions in early life.[4,14,17,19]

Intervention and Outcome Characteristics

Based on Table 3, the interventions used in the studies covered several main groups, namely microbiota-directed complementary foods, probiotics, synbiotics, prebiotics, legume-based therapeutic formulas, and ready-to-use therapeutic foods enriched with prebiotic components such as rice bran or galacto-oligosaccharides.[4,7,13–17,21,22] Comparators used included standard RUTF, RUSF, placebo, WHO F75/F100, fortified blended flour control, and other control formulas.[4,11–13,18,20,21] Most studies continued to provide standard

Table 2. Study characteristics

Author, year	Study design	Country	Sample size	Malnutrition category	Age range
Kerac, 2009[11]	Randomized controlled trial	Malawi	795; synbiotic n=399, control n=396	SAM	5-168 months
Grenov, 2017[12]	Randomized controlled trial	Uganda	400; probiotic n=200, placebo n=200	SAM	6-59 months
Chen, 2021[4]	Randomized controlled trial	Bangladesh	118 completed; MDCF-2 n=59, RUSF n=59	MAM	12-18 months
Barratt, 2022[14]	Single-blind placebo-controlled trial	Bangladesh	62; synbiotic n=21, probiotic n=20, placebo n=21	MAM	12-18 months
Nuzhat, 2023[7]	Randomized controlled trial	Bangladesh	67; placebo n=23, probiotic n=21, synbiotic n=23	SAM	2-6 months
Kambale, 2023[16]	Randomized controlled trial	Democratic Republic of Congo	400; probiotic n=200, placebo n=200	Uncomplicated SAM	6-24 months
Batool, 2023[15]	Randomized controlled trial	Pakistan	204; prebiotic n=102, placebo n=102	Uncomplicated SAM	Up to 60 months
Marconi, 2024[18]	Open-label age-stratified RCT	India	240; MDCF n=120, RUSF n=120	MAM	6-18 months
Calder, 2021[13]	Open-label randomized pilot trial	Uganda	58; cowpea n=20, inulin n=20, control n=18	SAM	>6 to <60 months
Hartman, 2024[17]	Randomized controlled trial	Bangladesh	124; MDCF-2 n=62, RUSF n=62	Post-SAM MAM	12-18 months
Barbazza, 2026[22]	Randomized controlled trial	Indonesia	200; RUTF n=105, RUTF + rice bran n=95	SAM or approaching SAM	6-59 months
Walsh et al., 2024[21]	Open-label phase II RCT	Uganda	160; legume feed n=80, WHO feed n=80	Hospitalized severe malnutrition	Median 17 months
Mostafa et al., 2024[19]	24-month secondary follow-up of RCT	Bangladesh	Parent RCT n=124; follow-up n=111-114	MAM	12-18 months at enrolment
Vray et al., 2024[20]	Three-arm open-label pragmatic RCT	Niger, Central African Republic, Senegal, Madagascar	881; control n=297, antibiotic n=290, prebiotic n=294	MAM	6-24 months

care according to local guidelines, such as F75, F100, RUTF, antibiotics, vitamin A, deworming, breastfeeding support, anthropometric monitoring, and inpatient or outpatient management according to the degree of malnutrition.[11–13,15–17,21,22] The follow-up duration varied from 28 days to 24 months, with most studies monitoring for 8 to 12 weeks.[12,13,16,19,20]

Outcomes assessed in the studies included nutritional recovery, weight gain, WLZ, WHZ, WAZ, LAZ, MUAC, time to recovery, mortality, diarrhea, pneumonia, readmission, adverse events, intestinal inflammatory biomarkers, microbiota composition, and growth-related plasma proteins.[4,7,15,16,18,21] The primary outcome showed that the MDCF intervention provided the most consistent benefits in improving anthropometric and microbiota-related biological profiles.[4,17,19] Studies by Chen, Hartman, and Mostafa showed that MDCF-2 improved WLZ, WAZ, MUAC, ponderal growth, linear growth trajectory, and microbiome features compared to RUSF.[4,17,19] Marconi's study also showed that MDCF was safe, acceptable, and provided a better recovery trend than RUSF.[18]

Results for probiotics, synbiotics, and prebiotics appear more variable. Grenov's study showed that the probiotics BB-12 and LGG did not improve weight gain or nutritional recovery in children with SAM, while Kambale's study showed that the combination of L. rhamnosus GG and L. reuteri DSM 17938 shortened the duration of diarrhea and accelerated initial recovery, although final recovery was similar to placebo.[12,16] Barratt and Nuzhat's study showed that B. infantis EVC001, both as a probiotic and as a synbiotic with LNnT, improved ponderal growth and several anthropometric parameters in infants with acute malnutrition.[7,14] The Batool and Barbazza studies support the potential of prebiotics or local food ingredients with prebiotic effects in improving weight gain, MUAC velocity, or hematological parameters, while the Calder, Walsh, and Vray studies showed more neutral results for the main outcomes.[13,15,20–22] Overall, both tables indicate that microbiota-based nutritional interventions have the potential to support growth recovery in children with acute malnutrition, but their effectiveness is highly dependent on

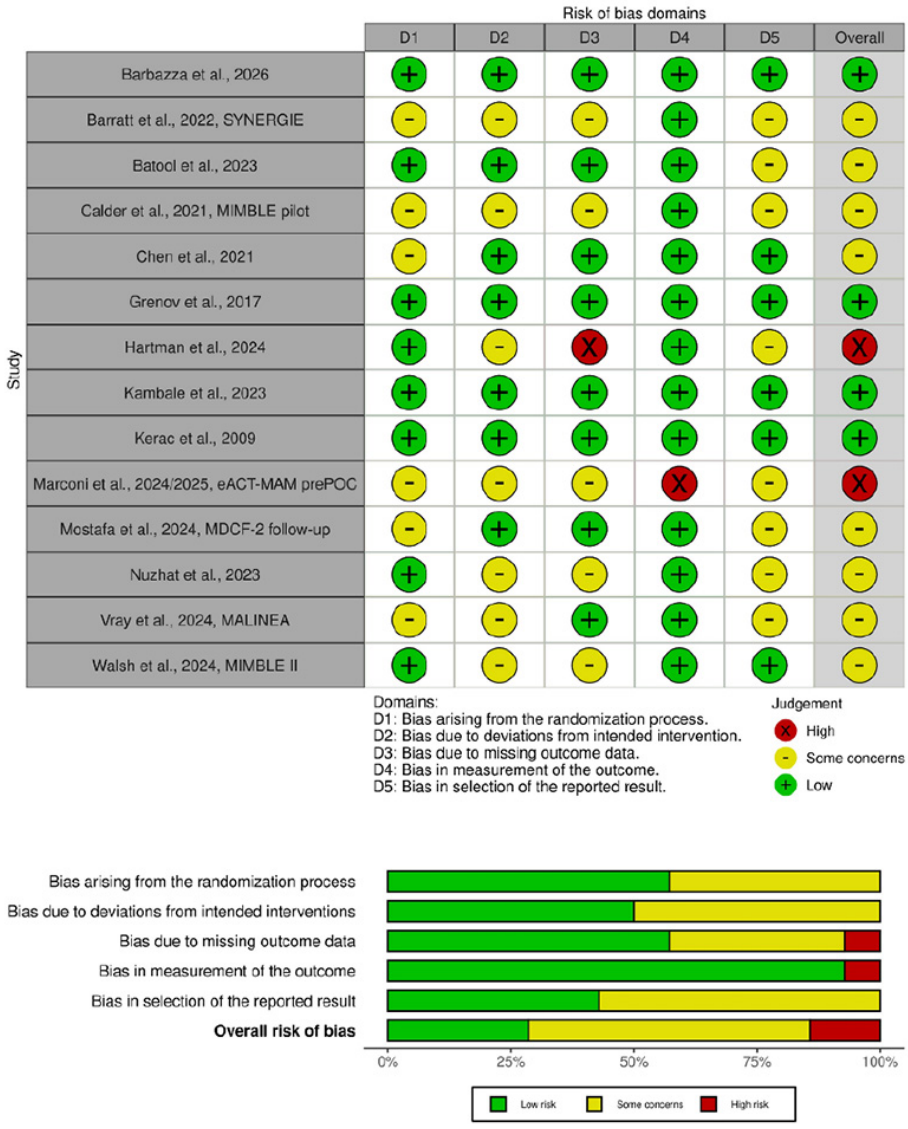


Figure 2. Risk of Bias.

the type of intervention, active ingredient composition, child age, malnutrition category, and follow-up duration.[4,18,20,21]

Risk of Bias

Based on the Cochrane RoB 2 assessment, the overall risk of bias in the 14 studies was dominated by the "some concerns" category, with 4 studies having a low risk, 8 studies having some concerns, and 2 studies having a high risk. The studies by Barbazza et al.,[22] Grenov et al.,[12] Kambale et al.,[16] and Kerac et al.[11] were assessed as having an overall low risk of bias, while those by Hartman et al.[17] and Marconi et al.[18] were assessed as having a high risk. The domain with the best assessment was outcome measurement, as most studies showed a low risk, while the main sources of concern came from deviations from the intended intervention, missing outcome data, and selection of reported outcomes. These results indicate that most studies are still suitable for use in narrative synthesis, but interpretation of findings requires caution, especially in studies with "some concerns" and "high risk of bias" (**Figure 2**).

DISCUSSION

This systematic review shows that nutritional interventions targeting the gut microbiota have the most consistent beneficial effects on growth recovery in children with acute malnutrition when designed as microbiota-based complementary foods, particularly microbiota-directed complementary foods or microbiome-directed therapeutic foods. The results of the 14 included studies showed a heterogeneous pattern of outcomes: MDCF interventions consistently improved anthropometric indices, including WLZ/WHZ, WAZ, MUAC, and ponderal growth rate, while probiotics, prebiotics, synbiotics, and legume-based formulas produced variable results that were frequently dependent on strain type, substrate, child age, degree of malnutrition, and duration of administration. Several studies, including Grenov et al., Kerac et al., Walsh et al., Calder et al., and Vray et al., reported neutral primary outcomes, indicating that microbiota-based interventions are not uniformly effective across all settings and populations.[11–13,20,21] These findings suggest that recovery from acute malnutrition depends not only on energy and protein supplementation but also on improvements in the gut ecology, which plays a role in nutrient absorption, mucosal immune maturation, and reduced intestinal inflammation. The review also shows that probiotics, prebiotics, and synbiotics have more variable benefits than MDCF, and their effectiveness appears to be strongly influenced by the strain, substrate, dose, duration of administration, and the readiness of the child's gut environment to accept new microbial colonization. These data are in line with previous systematic reviews reporting that microbiome-based interventions can improve growth outcomes in children aged 0 to 59 months in low- and middle-income countries, but evidence across intervention types remains heterogeneous.[8,9]

The findings regarding MDCF in this review align with the clinical trial by Chen et al., which demonstrated that MDCF-2 supports the recovery of children with moderate acute malnutrition and provides biological evidence that manipulation of microbiota components may be associated with improved growth.[4] A follow-up study by Mostafa et al. also supports these findings, as a 3-month MDCF-2 intervention in Bangladeshi children aged 12 to 18 months with MAM

Table 3. Population, intervention, and outcome characteristics

Author,year	Follow-up	Intervention	Comparator	Standard care	Outcomes	Main findings
Kerac, 2009[11]	Median treatment 33 days; outpatient follow-up until cure	RUTF + Synbiotic2000 Forte	Standard RUTF	National SAM protocol with F75, RUTF, antibiotics, and HIV care when indicated	Nutritional cure; mortality; weight gain; symptoms	Nutritional cure was similar between groups: 53.9% (215/399) in the synbiotic arm vs. 51.3% (203/396) in the control arm (p = 0.40). A subgroup analysis suggested a trend toward lower outpatient mortality in the synbiotic group (18/324 vs. 39/338; p = 0.06).
Grenov, 2017[12]	Inpatient phase plus outpatient treatment for 8-12 weeks	BB-12 + LGG probiotic, 10 billion CFU/day	Placebo sachet	WHO and Uganda SAM protocol with F75, RUTF or F100, antibiotics, and supportive care	Diarrhea days; recovery; weight gain; pneumonia; safety	No significant difference was observed in the primary outcome (diarrhea days) or in weight gain and nutritional recovery between the probiotic (BB-12 + LGG) and placebo groups.
Chen, 2021[4]	3-month intervention plus 1-month monitoring	MDCF-2 twice daily	RUSF	Breastfeeding and usual complementary feeding continued	WLZ, WAZ, MUAC, LAZ; microbiota; plasma proteins	MDCF-2 produced a significantly greater rate of WLZ change vs. RUSF: β = 0.021/week (95% CI 0.014–0.029) vs. 0.010/week (95% CI 0.003–0.017); between-group difference β = 0.011/week (95% CI 0.001–0.021). WAZ rate of change was also greater: β = 0.017/week (95% CI 0.012–0.022) vs. 0.010/week (95% CI 0.004–0.015); between-group difference β = 0.008/week (95% CI 0.001–0.015). MUAC rate of change did not differ significantly: between-group difference β = 0.003 cm/week (95% CI −0.001 to 0.007). LAZ did not differ significantly between groups.
Barratt, 2022[14]	4-week supplementation plus 4-week follow-up	B. infantis EVC001 with or without LNnT	Lactose placebo	Standard SAM management with F75, F100, feeding support, and routine NRU care	B. infantis abundance; anthropometry; intestinal inflammation	At study completion (day 56), WAZ was significantly higher in the probiotic (EVC001) arm compared to placebo (p = 0.002, Mann-Whitney U), and MUAC was also significantly greater (p = 0.015). WAZ was additionally higher in the synbiotic (EVC001 + LNnT) arm compared to placebo (p = 0.047).
Nuzhat, 2023[7]	4-week supplementation plus 4-week follow-up	B. infantis EVC001 probiotic or EVC001 + LNnT synbiotic	Lactose placebo	icddr,b SAM care with F75, F100, breastfeeding support, and follow-up	Weight gain; LAZ; WAZ; follow-up growth	The rate of weight gain in the probiotic arm was higher than placebo by 2.03 g/kg/day (p < 0.001) and by 1.13 g/kg/day in the synbiotic arm (p = 0.030). In linear mixed-effects model, mean WAZ was higher by 0.57 units in the probiotic arm vs. placebo (p = 0.018).
Kambale, 2023[16]	Biweekly follow-up for up to 12 weeks	L. rhamnosus GG + L. reuteri DSM 17938 with RUTF	Placebo oil + RUTF	CMAM-based SAM care with RUTF, amoxicillin, vitamin A, deworming, malaria, and HIV care	Diarrhea days; recovery; weight gain; mortality; safety	Mean days of disease were significantly lower in the probiotic group (4.11 days; 95% CI 3.37–4.51) vs. placebo (6.68 days; 95% CI 6.26–7.13; p < 0.001). In children ≥16 months, risk of diarrhea was lower in the probiotic arm (75.6%; 95% CI 66.2–82.9) vs. placebo (95.0%; 95% CI 88.2–97.9; p < 0.001). At week 6, 40.6% in the probiotic group were still awaiting recovery vs. 68.7% in placebo
Batool, 2023[15]	8 weeks with weekly outpatient follow-up	RUTF + galacto-oligosaccharides	RUTF + starch placebo	Outpatient CMAM with weekly anthropometry and clinical monitoring	Weight gain >15%; hematologic and biochemical outcomes	Children in the prebiotic arm gained approximately 20% of baseline weight over 8 weeks (mean weight: 5.44 ± 1.35 kg pre- to 6.53 ± 1.45 kg post-intervention; p < 0.005 vs. placebo). Significant between-group differences were also observed for MUAC, haemoglobin, haematocrit, platelet count, mean corpuscular volume, mean corpuscular haemoglobin, and albumin (all p < 0.005).
Marconi, 2024[18]	2-week run-in, 4-week intervention, 2-week follow-up	Shelf-stable MDCF twice daily	Isocaloric RUSF	Equal micronutrient mix, supervised feeding, and routine nutritional monitoring	Acceptability; safety; WLZ; WAZ; LAZ; MUAC; adverse events	Compliance and acceptability of the organoleptic properties were high across all three sites. Anthropometric outcomes (WLZ, WAZ, LAZ, MUAC) showed a trend favoring MDCF over RUSF, but this was a pre-proof-of-concept study and was not powered for efficacy
Calder, 2021[13]	28 days	Cowpea-enriched feed or inulin-enriched WHO feed	Standard F75/F100	Standard inpatient SAM care with antimicrobials and indicated treatment	Weight gain >5 g/kg/day; mortality; gut markers; microbiota	Most children in all three arms achieved weight gain >5 g/kg/day during hospitalization. No significant difference was observed between the legume feeds (cowpea or inulin-enriched) and standard F75/F100 for the primary outcome.
Hartman, 2024[17]	3-month intervention plus 1-month follow-up	MDCF-2 twice daily after acute rehabilitation	RUSF	Prior SAM rehabilitation with antibiotics, F75/F100, Khichuri Halwa, and breastfeeding support	Ponderal growth; WAZ; MUAC; microbiome; plasma proteins	MDCF-2 produced significantly greater ponderal growth (β-WLZ) compared to RUSF in post-SAM MAM children, consistent with findings from the primary MAM trial (Chen et al. 2021), despite MDCF-2 containing ~15% fewer calories per serving
Barbazza, 2026[22]	8-week intervention plus 8-week follow-up	RUTF + 5% stabilized rice bran	Standard RUTF	Indonesian SAM treatment with amoxicillin, vitamin A, deworming, and weekly monitoring	Weight; MUAC; z-scores; morbidity; compliance	RUTF with rice bran improved early weight and MUAC velocity, particularly in children aged 24–59 months. Significant between-group differences in weight and MUAC z-score trajectories were observed at early time points
Walsh et al., 2024[21]	Hospitalization phase with day 28 and day 90 follow-up	Lactose-free chickpea-enriched legume feed	WHO F75/F100	Inpatient SAM care; antibiotics or antimalarials as indicated; outpatient nutrition care after discharge	MUAC change; mortality; weight gain; diarrhea; readmission; serious adverse events	Day 90 MUAC increase was marginally lower in the legume feed (LF) arm vs. WHO feeds: 1.1 cm (IQR 1.1) vs. 1.4 cm (IQR 1.40; p = 0.09). Day 90 mortality was similar: 11/80 (13.8%) LF vs. 12/80 (15.0%) WHO feeds (OR 0.91; 95% CI 0.40–2.07; p = 0.83)
Mostafa et al., 2024[19]	24-month post-intervention follow-up	Prior MDCF-2 exposure in parent RCT	Prior RUSF exposure	Usual breastfeeding and complementary feeding during parent trial	Long-term WLZ, WAZ, LAZ, MUAC; microbiome; plasma proteins	Over 24 months of post-intervention follow-up, children previously receiving MDCF-2 showed sustained benefit in linear growth trajectory (LAZ) compared to the RUSF group, with significant differences maintained even after cessation of the intervention
Vray et al., 2024[20]	12 weeks with weekly follow-up	Fortified blended flour + inulin/FOS	Fortified blended flour control	Primary health centre care; free treatment and laboratory testing; albendazole when indicated	Nutritional recovery; MUAC; weight; height; diarrhea	The primary recovery endpoint (nutritional recovery at 12 weeks by MUAC) was not met for the prebiotic flour arm compared to the control flour arm. However, an exploratory analysis showed that WHZ-based recovery favored the prebiotic arm.

Abbreviations: CFU, colony-forming units; CMAM, community-based management of acute malnutrition; FBF, fortified blended flour; FOS, fructo-oligosaccharides; LAZ, length-for-age z-score; LGG, Lactobacillus rhamnosus GG; LNnT, lacto-N-neotetraose; MAM, moderate acute malnutrition; MDCF, microbiota-directed complementary food; MUAC, mid-upper arm circumference; NRU, nutritional rehabilitation unit; RCT, randomized controlled trial; RUSF, ready-to-use supplementary food; RUTF, ready-to-use therapeutic food; SAM, severe acute malnutrition; WAZ, weight-for-age z-score; WHZ, weight-for-height z-score; WLZ, weight-for-length z-score.

improved wasting during the intervention and reduced stunting during follow-up.[19] Hartman et al.'s study in children recovering from severe acute malnutrition extends this evidence, as microbiome-directed therapeutic food targets specific bacterial taxa and may be associated with improved growth in the post-SAM phase.[17] Theoretically, these results can be explained by MDCF's ability to provide a substrate that supports the growth of age-appropriate gut bacteria, enhances the production of functional metabolites, and improves microbiota interactions with the intestinal mucosa. These results may suggest greater efficacy than standard therapeutic foods that primarily focus on energy density, as standard RUTF or RUSF can improve body weight but may not necessarily restore complete microbiota maturation.[5,6]

The results of probiotics and synbiotics in this review are heterogeneous, reflecting the variability already observed in the results section across studies with different strain selections and populations. A study by Barratt et al. showed that Bifidobacterium infantis EVC001 increased weight gain in Bangladeshi infants with SAM and was associated with a reduction in intestinal inflammatory markers, supporting the concept that specific strains can improve recovery trajectories in acute malnutrition.[14] A study by Nuzhat et al. also reported that infants with SAM receiving probiotics had higher rates of weight gain compared to the synbiotic or placebo groups, although the improvement in LAZ was only a trend and not all outcomes reached statistical significance.[7] These results are partly in line with a study by Kambale et al., which supports the use of a combination of *Lacticaseibacillus rhamnosus* GG and *Limosilactobacillus reuteri* DSM 17938 in children with uncomplicated SAM, primarily through its potential impact on diarrhea in nutrition programs.[16] The differences in results between studies suggest that probiotics cannot be treated as a single, uniform class of interventions, as their biological effects depend on the strain's colonization ability, suitability to the local diet, the child's age, breastfeeding status, and the degree of intestinal mucosal damage. Systematic reviews by Heuven et al. and Addae et al. also showed a similar pattern, with some probiotic studies showing benefits on at least one growth outcome, but the overall evidence remains limited by variations in populations and interventions.[8,9]

Findings regarding prebiotics and locally sourced formulas offer interesting clinical potential, but the strength of evidence is lower than that for MDCF. Batool et al.'s study evaluated prebiotics as a synergistic adjunct to RUTF to improve anthropometric and hematological parameters in children with uncomplicated SAM in Pakistan, supporting the use of fermentable substrates as an additional component in malnutrition management.[15] Vray et al.'s study of children with MAM in several African countries tested a three-arm design including flour fortified with inulin/fructo-oligosaccharides (FOS) as the prebiotic arm; the antibiotic arm was not a microbiota-targeted nutritional intervention and was excluded from synthesis. The prebiotic arm provided field evidence that such strategies may be applicable in these settings, though the primary recovery endpoint was not met.[20] Walsh et al.'s study of children hospitalized with severe malnutrition in Uganda used a chickpea-based lactose-free formula and assessed MUAC and mortality through day 90, linking local foods, fermentable carbohydrates, and potential improvements in gut integrity.[21] Barbazza et al.'s study of Indonesian children with SAM and MAM used RUTF with rice bran, making this study relevant to rice-based countries and supporting the development of local ingredients with potential prebiotic effects.[22] These results align with theoretical reviews explaining that microbiota dysbiosis in malnutrition can impair nutrient absorption, short-chain fatty acid production, mucosal immunity, and resistance to enteropathogens.[13] However, the neutral primary outcomes observed in the Walsh et al., Calder et al., and Vray et al. studies in this review indicate that the field effectiveness of prebiotic and legume-based formulas remains inconsistent,[13,20,21] and clinical translation requires more standardized trial designs with gut microbiota and intestinal biomarkers as pre-specified outcomes.[1,5]

The strengths of this systematic review lie in its more specific focus on children with acute malnutrition, its separation of interventions based on microbiota-targeting mechanisms, and its simultaneous inclusion of growth, microbiota maturation, intestinal biomarkers, and clinical outcomes. This approach provides a more comprehensive picture than previous reviews, which often combined healthy children, stunted children, and children with various forms of undernutrition in a single synthesis. This systematic review has several limitations that warrant careful consideration. The stated search period and eligibility boundaries were not uniformly applied across all included studies, and the synthesis was further constrained by substantial heterogeneity in study designs, intervention types, outcome definitions, and follow-up durations, which precluded quantitative pooling and necessitated a narrative approach. The absence of a GRADE certainty-of-evidence assessment limits the ability to formally translate findings into clinical recommendations, and the lack of a prospectively registered protocol reduces transparency regarding potential deviations from a pre-specified analysis plan. These limitations collectively underscore the need for future systematic reviews in this area to adopt more rigorous and consistent methodological standards, including prospective registration, standardized outcome reporting, and formal certainty grading.

CONCLUSION

Nutritional interventions targeting the gut microbiota have the potential to support growth recovery in children with acute malnutrition, particularly microbiota-directed complementary food interventions, which demonstrated more consistent improvements in WLZ/WHZ, WAZ, MUAC, ponderal growth, and microbiota profiles compared to standard interventions. Probiotics, synbiotics, prebiotics, and locally sourced food formulas also demonstrated benefits on several outcomes, but results varied according to strain type, substrate composition, child age, malnutrition severity, duration of administration, and length of follow-up. Future studies are

recommended to utilize randomized clinical trial designs with larger sample sizes, uniform outcome definitions, long-term follow-up, and integrated measurements of anthropometry, microbiota, intestinal biomarkers, clinical events, and intervention safety to strengthen the evidence base for clinical implementation.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ETHICAL CLEARANCE

Not applicable.

INFORMED CONSENT

Not applicable.

AUTHOR CONTRIBUTIONS

RNS initiated the study, collected and curated the data, performed the analysis, and wrote the initial draft; IWG and IGLS designed the methodology, supervised the study, validated the findings, and edited the manuscript; IGLS supervised the study, validated the findings, and edited the manuscript; RNS and IGLS contributed to data interpretation and critically revised the manuscript. All authors reviewed and approved the final manuscript and take responsibility for the integrity and accuracy of the work.

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DISCLOSURE OF USE OF GENERATIVE AI

Generative AI-assisted technology was used only to support language refinement, formatting, and editorial improvement of the manuscript. The authors reviewed, verified, and approved all final content and take full responsibility for the integrity and accuracy of the manuscript.

DATA AVAILABILITY STATEMENT

The data extraction forms, Risk of Bias 2 assessments, and PRISMA 2020 checklist are available from the corresponding author upon reasonable request.

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