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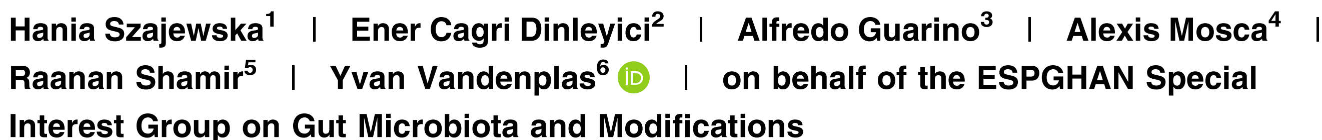
REVIEW ARTICLE

Nutrition

Technical review by the ESPGHAN Special Interest Group on Gut Microbiota and Modifications on the health outcomes of infant formula supplemented with postbiotics



Hania Szajewska[1] | Ener Cagri Dinleyici[2] | Alfredo Guarino[3] | Alexis Mosca[4] | Raanan Shamir[5] | Yvan Vandenplas[6] | on behalf of the ESPGHAN Special Interest Group on Gut Microbiota and Modifications

Correspondence
Yvan Vandenplas, KidZ Health Castle, UZ Brussel, Laarbeeklaan 101, 1090 Brussels, Belgium.
Email: Yvan.Vandenplas@uzbrussel.be

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Abstract

This technical review, one of five developed by the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) Special Interest Group (SIG) on Gut Microbiota and Modifications (GMM), supports the creation of a Paper on the use of biotic-supplemented formulas, including those containing postbiotics. Postbiotics are defined as inanimate [i.e., dead, nonviable] microorganisms and/or their components that confer health benefits to the host. This review focuses on the clinical outcomes of infant formulas supplemented with postbiotics. The SIG-GMM conducted technical review to evaluate the clinical outcomes of postbiotic-supplemented infant formulas in healthy infants (0–12 months) published before 2024. Based on the findings of a technical review, all members of the SIG voted anonymously on statements related to clinical outcomes with a score between 0 and 9. A score higher than 6 indicated agreements. A statement was rejected if <75% of the members agreed. Twelve randomized controlled trials (RCTs) met the inclusion criteria. The postbiotics studied so far showed no difference compared to the control formula in outcomes such as anthropometric data, gastrointestinal symptoms, stool characteristics, allergy, infections, tolerability and safety. The RCTs evaluating postbiotics added to infant formula are heterogeneous due to differences in study design, variations in postbiotics and durations of interventions. The studies were powered to demonstrate and did show that there was good tolerance and adequate, safe growth comparable to nonsupplemented formula in presumed healthy infants. This technical review provides the foundation for recommendations on the use of postbiotic-supplemented infant formulas in healthy infants.

KEYWORDS

breast feeding, fermented formula, formula feeding, infant feeding

For affiliations refer to page 287.

See related articles, pages 1-3, 224-235, 236-245, 246-262, 263-288, 300-315.

For a complete list of the ESPGHAN Special Interest Group on Gut Microbiota and Modifications members, see the Acknowledgments section.

[Correction added on 02 December 2025, after the first online publication: Article format has been updated.]

Hania Szajewska and Ener Cagri Dinleyici contributed equally to this study.

Disclaimer: ESPGHAN is not responsible for the practices of physicians and provides guidelines and position papers as indicators of best practice only. Diagnosis and treatment is at the discretion of physicians. Although this paper is produced by the ESPGHAN Special Interest Group on Gut Microbiota and Modifications it does not necessarily represent ESPGHAN policy and is not endorsed by ESPGHAN.

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1 | INTRODUCTION

Postbiotics refer to inanimate (i.e., dead, nonviable) microorganisms and/or their components that confer health benefits to the host, as defined by the International Scientific Association for Probiotics and Prebiotics.[1] Infant formulas containing postbiotics are available since many years; however, they were previously considered as "fermented formula," as they are produced through a fermentation process using lactic acid-producing bacteria and/or Bifidobacteria. This production process yields an end-product with a minimal amount of live bacteria. These fermented products undergo physical processes such as homogenization, pasteurization, sterilization and spray-drying.[2] The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) published a position paper on the use of fermented infant formulas in 2007.[2] The 2007 ESPGHAN position paper reviewed limited evidence on fermented infant formulas, identifying two randomized controlled trials (RCTs) with 933 infants. While some findings suggested a potential reduction in infectious diarrhea, the data were insufficient to draw general conclusions. The paper emphasized the need for further RCTs to assess their effects.[2] Accumulating new evidence and the updated definition prompted the ESPGHAN Special Interest Group (SIG) on Gut Microbiota and Modification (GMM) to re-evaluate the clinical outcomes of infant formulas supplemented with postbiotics. Since then, accumulating evidence on the clinical effects, safety, and mechanisms of postbiotic-supplemented formulas, along with an updated definition of postbiotics, prompted the ESPGHAN SIG-GMM to re-evaluate their use. Although this paper is produced by the ESPGHAN SIG on GMM it does not necessarily represent ESPGHAN policy and is not endorsed by ESPGHAN.

What is Known

- Postbiotics are inanimate (nonviable) microorganisms or their components that may provide health benefits to the host.
- Postbiotic-supplemented formulas were previously referred to as "fermented formulas" because they were primarily obtained through fermentation. These formulas are widely available, though their routine use remains debated.

What is New

- A review of 12 randomized controlled trials shows that postbiotic-supplemented formulas are well-tolerated, support normal growth, and pose no safety concerns.
- However, consistent clinical benefits have not been demonstrated across studies, and variability in study designs and outcomes limits clear conclusions on efficacy.
- This technical review underpins recommendations for using postbiotic-supplemented formulas in healthy infants.

2 | METHODS

This technical review is one of five developed by the ESPGHAN SIG-GMM to support the development of a Position Paper on the use of postbiotic-supplemented infant formulas. Our priority research questions: (i) "Are there, and if so which, clinically relevant benefits have been demonstrated by the supplementation with any biotic to infant formula?", (ii) "Should biotics be added to infant formula? If yes, which specific biotic and for which indications?" This technical review aims to support the development of a position paper on the use of postbiotic-supplemented infant formula.

The search was conducted up to December 31, 2023, across Cochrane, DARE, CENTRAL, PubMed, and EMBASE, and complemented with searches on ClinicalTrials.gov. Search terms included: "infant formula," "follow-on formula," "non-supplemented formula," and "postbiotic" or "fermented". Only English-language papers were included except for one paper in French, which was included. Peer-reviewed RCTs, meta-analyses, systematic reviews, and previous ESPGHAN recommendations have been used for our analyses. The reference lists from identified studies and key review articles, including previously published meta-analyses, have also been evaluated.

We only included RCTs that evaluated healthy term-born infants under 1 year old who were receiving infant formula. Studies comparing postbiotic-supplemented infant formula to non-supplemented formula or human milk in healthy infants were included. Thickened anti-regurgitation formulas were included because infant regurgitation is a common and benign physiological phenomenon in early life, and such formulas are used as part of standard infant feeding practices. Studies where postbiotics were introduced after manufacturing or used in hydrolyzed formulas were excluded. We excluded studies that dealt with preterm infants, cow's milk allergy, or any condition or disease. We performed an initial screening of the title, abstract, and keywords of every identified record. The next step was the retrieval of the full text of potentially relevant publications. At least two reviewers independently assessed the eligibility of each potentially relevant trial with the use of inclusion criteria. Figure 1 displays a flow chart detailing the study selection process in accordance with PRISMA guidelines.[3]

Data extraction focused on study characteristics, fermentation or other procedures, intervention details, and follow-up duration. Outcomes evaluated included

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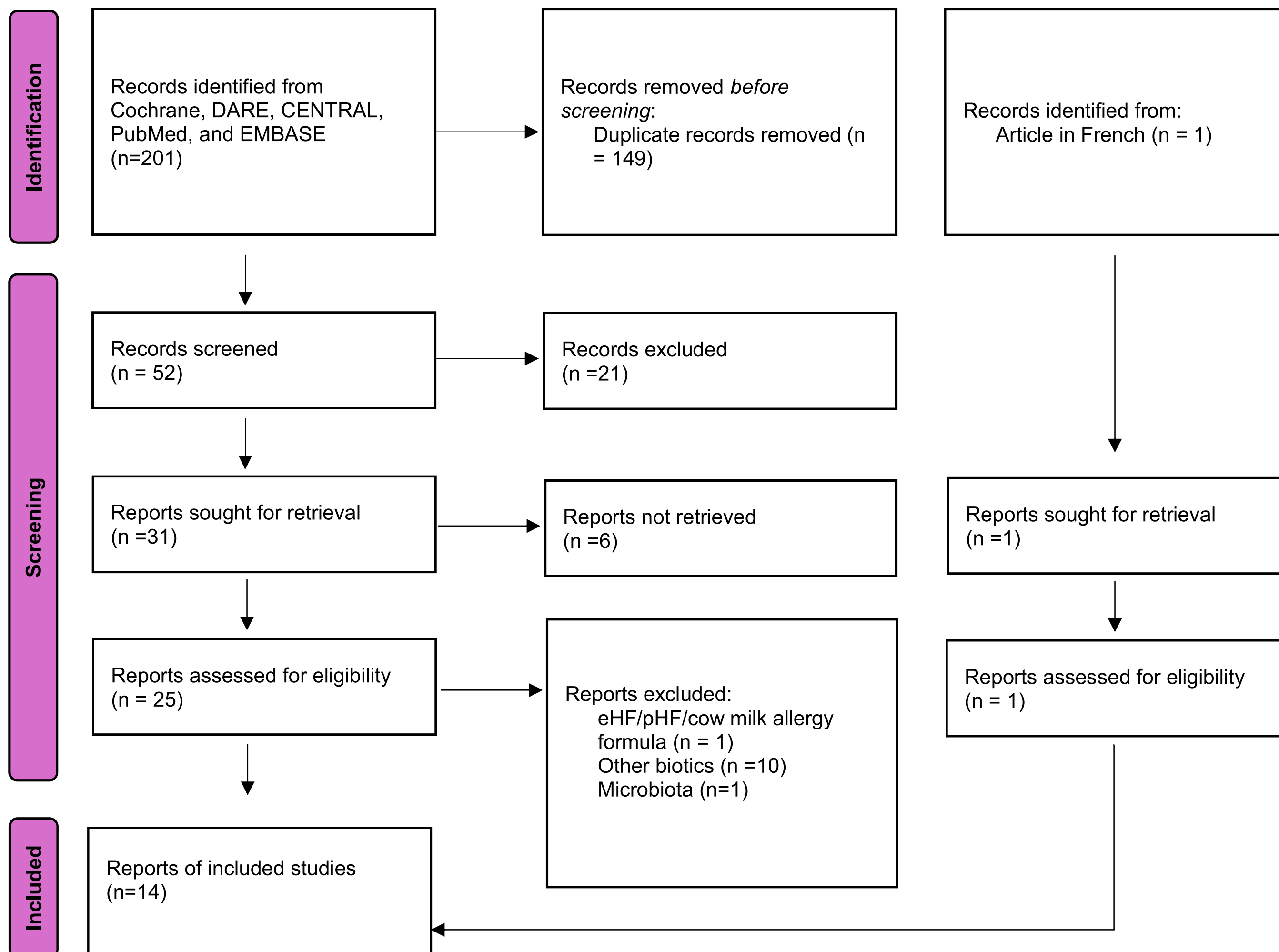

FIGURE 1 Flow chart of identification of studies.

anthropometric measurements, gastrointestinal symptoms, stool frequency and consistency, allergy prevention, infection prevention, and safety/tolerability. Microbiota composition was not a priority focus of this technical report and therefore was not discussed.

The risk of bias was assessed using the Cochrane tool.[4] Consensus on statements was established via a modified Delphi process[5] requiring 75% agreement.

All members of the SIG ($n = 20$) voted anonymously on each statement. The assessment was conducted according to a pre-defined protocol, ensuring a structured and consistent evaluation process. The expert votes are already summarized in the "Statement" section. Presenting the votes by supplementation category was not part of the original methodology.

3 | RESULTS

The outcomes from 12 RCTs, reported in 14 publications, were included (Table 1). Additionally, we identified two systematic reviews.[11,12]

Ten reviewed RCTs focused on healthy infants from birth or shortly after, and two RCTs included infants with troublesome regurgitation. One RCT included infants aged 4–6 months.[17] Strains such as *Bifidobacterium (B.) breve* C50 and *Streptococcus (S.) thermophilus* 065 were most used for fermentation, with variations in the fermentation process and formula modifications, including the addition of prebiotics (short chain galacto-oligosaccharides (scGOS)/long chain fructo-oligosaccharides (lcFOS) in a 9:1 ratio), 3′-galactosyllactose (3′-GL), and fucosyllactose (2′-FL). The duration of the interventions varied from 15 days to 12 months. Most studies had two formula groups; however, two RCTs (reported in three publications) had four groups.[6,17,18] In one RCT, *Lactobacillus paracasei* (now renamed as *Lacticaseibacillus (L.) paracasei* CBA L74 was used for fermentation.[7] One RCT evaluated a formula with reduced protein content, a lower casein-to-whey protein ratio (due to increased α-lactalbumin content) and double the usual amount of docosahexaenoic acid/arachidonic acid. Additionally, this formula included a thermally

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TABLE 1 Randomized controlled trials with infant formula supplemented with postbiotics reporting clinical outcomes.

Publication	Study design	HMO analogs	Study period	Study population	Study duration
Mullié et al.,[6] France	DBRCT	*B. breve* C50 and *S. thermophilus* 065	August 1999 and January 2000	Postbiotic formula ($n = 11$) Control formula ($n = 9$)	4 months
Indrio et al.,[7] Italy	DBRCT	*B. breve* C50 and *S. thermophilus* 065	-	Postbiotic formula ($n = 30$) Control formula ($n = 30$) Breastfed ($n = 30$)	4 months
Roy et al.,[8] France	DBRCT	*B. breve* C50 and *S. thermophilus* 065	-	Postbiotic formula ($n = 47$) Control formula ($n = 46$)	4 months
Morisset et al.,[9] France	DBRCT, multicenter	*B. breve* C50 and *S. thermophilus* 065	January 2004 to April 2006	Postbiotic formula ($n = 66$) Control formula ($n = 63$)	24 months
Thibault et al.,[10] France	DBRCT, multicenter	*B. breve* C50 and *S. thermophilus* 065	-	Postbiotic formula ($n = 464$) Control formula ($n = 449$)	5 months
Huet et al.,[5] Vandenplas et al.,[11] 2016, France, Belgium, Ireland	Prospective, DB, RCT, parallel-group, multicente controlled equivalence trial.	*B. breve* C50 and *S. thermophilus* 065; 15% FERM and 50% FERM with or without scGOS/lcFOS (9:1)	October 2010 and September 2012	scGOS/lcFOS ($n = 109$) scGOS/lcFOS + 15% FERM ($n = 111$) scGOS/lcFOS + 50% FERM ($n = 107$) 50% FERM ($n = 104$)	4 months
Béghin et al.,[12] France, Germany, Italy	Prospective, DB, RCT, four-arm parallel group, multicentre study	*B. breve* C50 and *S. thermophilus* 065scGOS/lcFOS (9:1) *B. breve* C50 and *S. thermophilus* 065+ scGOS/lcFOS	February 2011 and April 2012	*B. breve* C50 and *S. thermophilus* 065 ($n = 70$) scGOS/lcFOS ($n = 70$) *B. breve* C50 and *S. thermophilus* 065 + scGOS/lcFOS ($n = 70$) Control formula ($n = 70$) Breastfed ($n = 70$)	6 months
Rodriguez-Herrera et al.,[13,14] Italy, Spain	Prospective, DB, randomized, explorative trial	*B. breve* C50 and *S. thermophilus* 065scGOS/lcFOS (9:1)	June 2012 to December 2013	Postbiotic formula ($n = 72$) Control formula ($n = 80$) Breastfed ($n = 72$)	17 weeks
Bellaiche et al.,[15] Poland, France, Germany	DBRCT Multicenter	0.4 g/100 mL scGOS/lcFOS (ratio 9:1) 26% fermented formula with postbiotics *B. breve* C50 and *S. thermophilus* 065	November 2017 and July 2019	Postbiotic formula ($n = 92$) Control formula ($n = 80$)	4 weeks
Vandenplas et al.,[16] Belgium, Hungary, Poland, Spain, Ukraine	DBRCT two-arm parallel growth equivalence trial.	0.8 g/100 mL scGOS/lcFOS (ratio 9:1) 26% fermented formula with postbiotics *B. breve* C50 and *S. thermophilus* 065 + 2′FL (0.1 g/100 ml)	June 2018 and April 2019	Experimental formula ($n = 101$) Control (prebiotic) formula ($n = 95$) Breastfed group ($n = 58$)	17 weeks

(Continues)

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TABLE 1 (Continued)

Publication	Study design	HMO analogs	Study period	Study population	Study duration
Roggero et al.,[17] Italy	DBRCT	*Lacticaseibacillus paracasei* CBA L74	September 2015 and April 2016	Postbiotic formula ($n = 26$) Control formula ($n = 26$) Breastfed group ($n = 26$)	3 months
Plaza-Dias et al.,[18] Spain	DBRCT	*Bifidobacterium animalis subsp. lactis* BPL1 HT (heat treated)	October 2018 and November 2020	Postbiotic formula ($n = 62$) Control formula ($n = 65$) Breastfed group ($n = 59$)	12 months

Abbreviations: 2′-FL: 2′ fucosyllactose; B. breve: *Bifidobacterium breve*; DBRCT, double blind randomized controlled trial; lcFOS: long chain fructo oligosaccharides; S. thermophilus: *Streptococcus thermophilus*; scGOS: short chain galacto-oligosaccharides.

inactivated postbiotic (*B. animalis* subsp. *lactis*, BPL1TM HT).[8] The risk of bias is summarized in Table 2.

3.1 | Formula fermented with *B. breve* C50 and *S. thermophilus* 065

Five RCTs reported on infant formulas fermented with *B. breve* C50 and *S. thermophilus* 065 without any additional modifications,[6–10] administered during the first 4 months of life.[9,10,13,15] RCT[14] included infants aged 4–6 months. Additionally, two RCTs[8,15] provided data on an infant formula that was thickened with starch (in one RCT, the fermented formula also contained also scGOS and lcFOS.[16] We included one French-language paper was an exception,[15] as its content was deemed particularly relevant to the review. While we recognize this as a limitation, we believe it does not significantly impact the overall conclusions of the study.

3.1.1 | Anthropometry

Compared with non-supplemented formula, the use of formulas fermented with *B. breve* C50 and *S. thermophilus* 065 resulted in all RCTs in similar growth parameters as in control groups.

3.1.2 | Gastro-intestinal symptoms

One RCT ($n = 109$) found that thickened fermented formula has the potential to reduce the intensity and frequency of not well-defined, digestive symptoms related to gas frequency and intensity.[16]

3.1.3 | Infection

A large RCT, evaluating 913 out of 971 randomized infants, found no significant difference in diarrhea duration, number of episodes, or hospital admissions between groups receiving formula fermented with *B. breve* C50 and *S. thermophilus* and regular infant formula.[14] However, there was a significant difference in the severity of diarrhea, as measured by the dehydration rate, with fewer medical consultations, fewer oral rehydration solution prescriptions, and fewer changes of formula.[14]

3.1.4 | Allergy

Based on the findings from one RCT ($n = 129$), the use of formula fermented with *B. breve* C50 and *S.*

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TABLE 2 Risk of bias assessment.

Publication	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Béghin et al.[12]	LR	LR	LR	LR	LR	LR	Unclear
Bellaiche et al.[15]	LR	HR	LR	LR	LR	LR	Unclear
Huet et al.,[5] Vandenplas et al.[11]	LR	Unclear	Unclear	LR	LR	LR	Unclear
Indrio et al.[7]	Unclear	Unclear	Unclear	Unclear	LR	LR	Unclear
Morisset et al.[9]	LR	LR	LR	LR	LR	LR	Unclear
Mullié et al.[6]	LR	LR	LR	LR	LR	LR	Unclear
Plaza-Dias et al.[18]	LR	LR	LR	LR	LR	LR	Unclear
Rodriguez-Herrera et al.[13,14]	LR	Unclear	LR	LR	HR	LR	Unclear
Roggero et al.[17]	LR	LR	LR	LR	LR	LR	Unclear
Roy et al.[8]	HR	HR	HR	HR	Unclear	Unclear	Unclear
Thibault et al.[10]	HR	HR	HR	HR	Unclear	Unclear	Unclear
Vandenplas et al.[16]	LR	LR	LR	LR	Unclear	Unclear	Unclear

Abrreviations: HR, high risk; LR, low risk.

TABLE 3 Statements.

Statement		Median/Mean	Votes
1	Infant formula containing postbiotics studied so far°, was shown to be safe and result in appropriate growth in presumed healthy, non-exclusively breastfed infants.	9/8.9	8 (3x)/9 (17x)
2	Infant formulas containing postbiotics, studied so far°, in presumed healthy, non-exclusively breastfed infants, have not consistently demonstrated clinical benefits.	9/8.5	6; 7(2x); 8 (2x); 9 (15)

Note: °: the list of postbiotics studied so far can be found in the document.

thermophilus was not effective for preventing cow's milk allergy.[13]

3.2 | Partly fermented (30%) postbiotic formula with *B. breve* C50 and *S. thermophilus* 065, combined with prebiotics (scGOS/lcFOS at a 9:1 ratio)

One RCT reported in two publications comparison of the effects of a partly fermented postbiotic infant formula containing *B. breve* C50 and *S. thermophilus* 065, along with a mixture of 0.8 g/100 mL of scGOS and lcFOS (in a 9:1 ratio), against a standard infant formula and a breastfed reference group.[19,20] The study population at inclusion consisted of 224 out of 300 (75%) randomized healthy, term-born infants up to 17 weeks of age from Italy and Spain. None of the clinical outcomes were defined as the primary outcome.

3.2.1 | Anthropometry

The growth parameters, including mean weight-for-age, length-for-age, weight-for-length, and head circumference-for-age, were similar between the formula groups, indicating adequate growth. Both formula groups showed higher head circumference gains compared to the breastfed reference group.[19,20]

3.2.2 | Gastrointestinal symptoms

There was no significant difference between the post-biotic and control groups in parent-reported incidence of moderate or severe gastrointestinal symptoms. The incidence of these symptoms decreased over time in both formula-fed groups and the breastfed reference group.[19,20]

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3.2.3 | Stool consistency and frequency

Infants consuming the experimental formula had stool consistency values closer to that of breastfed infants and higher stool frequency from 9 weeks of age onwards compared to the control group. There was a higher incidence of diarrhea in the postbiotic group according to World Health Organization (WHO) criteria ($p < 0.05$ at 10, 12, and 17 weeks of age). The overall incidence of constipation was very low.[19,20]

3.2.4 | Adverse effects

No significant differences were observed between the formula groups in the percentage of serious adverse events (SAEs), and none of the SAEs were related to the intake of the study product.[19,20]

3.3 | Prebiotic and/or postbiotic formulas with *B. breve* C50 and *S. thermophilus* 065 with varying degrees of fermented content (15% and 50%) with and without prebiotics (scGOS/lcFOS)

One double-blind RCT reported in two publications compared the effects of four interventions[17,18]:

- A non-fermented formula with prebiotics (scGOS/lcFOS).
- A formula containing 15% fermented formula with postbiotics *B. breve* C50 and *S. thermophilus* (Lactofidus™) fermentation process and prebiotics.
- A formula with 50% fermented content and prebiotics.
- A formula with 50% fermented content without prebiotics.

While this study examined formulas containing different ratios of fermented and non-fermented components, the study is relevant to our technical review because the fermented fractions used in these formulas contain non-viable microbial components, which align with the updated definition of postbiotics; and provides valuable insights into the clinical effects of postbiotic-containing formulas.[17] The study was conducted in three countries (France, Belgium, and Ireland) and randomized 432 healthy infants with a gestational age of 37–42 weeks, a birth weight of 2.5–4.5 kg, and a postnatal age of less than 28 days. Out of the participants, 276 completed the study until 17 weeks of age and were included in the analyses.

3.3.1 | Anthropometry

Huet et al.[17] reported data on the primary outcome which was daily weight gain during the intervention (equivalence criterion: difference in daily weight gain ≤3 g/day). Equivalence of weight gain per day was demonstrated in both the intention-to-treat and per-protocol analyses. No differences between groups were observed in other growth parameters, formula intake, and the number or severity of adverse events.[17]

3.3.2 | Gastrointestinal symptoms

Over the study period, all symptom scores for gastrointestinal symptoms were reported as mild across all study arms. However, at 8 weeks, the group fed with the formula containing 50% fermentation and prebiotics had a higher average symptom score for flatulence compared to other groups.[17]

3.3.3 | Stool consistency and frequency

In terms of stool consistency, the 50% fermentation plus prebiotics group consistently showed lower stool consistency scores compared to the 50% fermented formula without prebiotics across various age points. This was especially notable at 8 weeks of age. There were no significant differences in stool frequency between the study arms throughout the study.[17]

3.3.4 | Other

According to the second publication results at 4 weeks (but not at other time points) showed a significant reduction in the number of crying episodes per day with the formula containing 50% fermentation and prebiotics compared to the 50% fermented formula without prebiotics.[18] There were no significant differences in sleep episodes or duration. A lower incidence of investigator-reported infantile colic was noted in the postbiotic group compared to the control group (1.1% vs. 8.7%, respectively; $p < 0.02$).[18]

3.4 | Postbiotic formulas with *B. breve* C50 and *S. thermophilus* 065: Varying fermentation levels and prebiotic (scGOS/lcFOS)

One RCT assessed 280 term-born infants fed with one of three experimental formulas against a non-supplemented control formula and breast-fed infants over a period of 6 months.[6]

- Combined bioactive compounds from specific fermentation (FERM) with a 9:1 mixture of scGOS and lcFOS prebiotics.

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- Non-supplemented formula supplemented with a 9:1 mixture of scGOS and lcFOS prebiotics only.
- Non-supplemented formula enriched with bioactive compounds from FERM but without additional prebiotics.

3.4.1 | Anthropometry

There were no differences in mean weight, length, or head circumference between any of the experimental formula groups, the control group, and the breastfed reference group, with all being within the normal range of WHO Growth Standards.

3.4.2 | Stool consistency and frequency

At 2 and 4 months, infants fed the FERM/scGOS/lcFOS formula had significantly softer stools compared to the control group, aligning more closely with those of breastfed infants. However, these differences were not present at 6 months of age. Stool frequency was significantly higher in all experimental formula groups compared to the control group at 4 months but not at 2 or 6 months.[6]

3.4.3 | Adverse events

The numbers and types of adverse events were similar in the experimental and control groups.[6]

3.5 | Partly (26%) postbiotic fermented formula with *B. breve* C50 and *S. thermophilus* 065, prebiotics (scGOS/lcFOS 9:1), and bioactive compounds 3′-GL, 2′-FL, along with milk fat

The 2020 study by Vandenplas et al.,[21] known as the VOYAGE study, was a double-blind, randomized, controlled, multi-country trial assessing the effects of a partly fermented infant formula with postbiotics, specific oligosaccharides, 2′-FL, and milk fat on 215 healthy term infants from Belgium, Hungary, Poland, Spain, and Ukraine.[21]

3.5.1 | Anthropometry

The study confirmed equivalence in weight gain, length, and head circumference between the infants fed with the study formula and those fed with the control formula. The study formula supported adequate infant growth, aligning with WHO growth standards, which was also comparable to the breastfed reference group.

3.5.2 | Gastrointestinal symptoms

There were no statistically significant differences observed in adverse events or gastrointestinal tolerance between the study groups.

3.5.3 | Adverse events

All serious adverse events were considered unrelated or unlikely to be related to the study product. The incidence of adverse events was similar between the test group and the control group, with no significant differences in the number or type of adverse events reported.[21]

3.6 | Partly fermented anti-regurgitation formula with *B. breve C50* and *S. thermophilus* and prebiotics

One RCT involving 182 infants diagnosed with uncomplicated regurgitation based on adapted Rome IV criteria assess the effects of a formula containing 0.4 g/100 mL of locust bean gum (LBG) as thickener, 0.4 g/100 mL scGOS/lcFOS (ratio 9:1) and 26% fermented formula with postbiotics *B. breve* C50 and *S. thermophilus* (Lactofidus™) fermentation process, which included 3′-GL.[16] The control product contained 0.4 g/100 mL LBG and 11% fermented formula with postbiotics but did not contain scGOS/lcFOS. The study lasted for 4 weeks, with an optional extension phase of another 4 weeks.[16]

3.6.1 | Anthropometry

The growth metrics such as weight-for-age, length-for-age, weight-for-length, and head circumference-for-age WHO z-score values were not statistically different between the study groups.[16]

3.6.2 | Stool consistency and frequency

No significant differences were found between the study groups in stool frequency, consistency, and episodes of diarrhea. Most infants had “soft” stools, with a small proportion having watery or hard stools.

3.6.3 | Adverse events

Adverse events reported during the 8-week study period were predominantly gastrointestinal disorders, infections, and skin disorders. There was a relatively higher number of AEs in the control group compared to

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the test group, with gastrointestinal disorders being more common in the control group. Skin disorders were more frequent in the test group but were not considered related to the product by the investigators. There were no significant differences in the use of medication between the groups.[16]

Other: The Infant Gastrointestinal Symptom Questionnaire sum score was the primary outcome, which included bowel movements, vomiting, spitting, crying, and fussiness. The 4-week Infant Gastrointestinal Symptom Questionnaire sum score was similar in both groups.[16]

3.7 | Formula fermented with *L. paracasei* CBA L74

One double-blind placebo controlled RCT investigated the effects on immune defense mechanisms (primary endpoint: secretory IgA, antimicrobial peptides), the microbiota and its metabolome (secondary outcomes) of formula fermented with *L. paracasei* CBA L74 compared with non-supplemented formula and breastfed infants over a period of 3 months.[7] All clinical outcomes were reported as secondary outcomes.

3.7.1 | Anthropometry

Anthropometric measurements taken at various study points showed no statistically significant differences between the two formula groups. Both formulas supported similar infant growth, body composition at enrollment and at 3 months.[7]

3.7.2 | Gastrointestinal symptoms

Both study formulas were well-tolerated, with no differences in the prevalence of gastrointestinal symptoms (spitting, vomiting, colic, and daily stool frequency) observed throughout the study.[7]

3.7.3 | Adverse events

Adverse events were recorded throughout the study period, but these data were not shown.

3.8 | Low protein formula with thermally inactivated *B. animalis* subsp. *lactis* BPL1TM HT

A blinded RCT enrolled infants under 21 days old to compare a low-protein formula with a lower casein-to-whey protein ratio and enhanced levels of docosahexaenoic acid/arachidonic acid, and the addition of thermally inactivated *B. animalis* subsp. *lactis*, BPL1TM HT ($n = 70$).[8] This group was compared with infants receiving a non-supplemented infant formula ($n = 70$). An exclusively breastfed group ($n = 70$) served as a reference.

3.8.1 | Anthropometry

Both formula groups had higher weight gain than the breastfed group at 6 and 12 months, with no significant differences between the two formula groups. Length, head circumference, and skinfold measurements were similar across all groups. The low protein postbiotic formula met WHO standards for weight gain and body composition.[8]

3.8.2 | Gastro-intestinal symptoms

The non-supplemented formula group reported more gastrointestinal symptoms. Digestive tolerance and infant behavior were similar across all groups.

3.8.3 | Stool consistency and frequency

The breastfed group showed more liquid stool consistency. No other differences were documented.

3.8.4 | Infection

Bronchitis, and bronchiolitis were less prevalent in the low protein postbiotic formula group compared to the non-supplemented formula group.[8]

3.8.5 | Allergy

Atopic dermatitis was less prevalent in the low-protein postbiotic formula group compared to the non-supplemented formula group.[8]

4 | CONCLUSIONS

The evaluated infant formulas containing postbiotics have been found to be safe and generally well-tolerated by infants who are not breastfed (Table 3; Statements 1 and 2). Nonetheless, clinical benefits have not been consistently demonstrated across studies. While some studies suggest gastrointestinal benefits, the outcomes were not homogenously defined (e.g., diarrhea definition and digestive symptoms) and were not conclusively established.

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Additionally, no single study evaluated more than one specific postbiotic preparation, limiting the generalizability of the findings to other postbiotic preparations. This lack of consistency in study design and outcome definitions makes it challenging to draw definitive conclusions about the efficacy of postbiotics in infant formulas. Moreover, the diverse types of postbiotics and variations in their formulations add further complexity to interpreting the clinical impact on non-breastfed infants. Future research should aim to standardize outcome measures and include comparisons across multiple postbiotic formulations to better understand their potential benefits. This technical review provides the foundation for recommendations on the use of postbiotic-supplemented infant formulas in healthy infants.

AFFILIATIONS

[1]Department of Paediatrics, The Medical University of Warsaw, Warsaw, Poland

[2]Department of Pediatrics, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey

[3]Department of Maternal and Child health, Pediatric Infectious Disease Unit, University Hospital "Federico II", Naples, Italy

[4]Department of Pediatric Gastroenterology and Nutrition, Robert-Debré Hospital, Paris, France

[5]Institute of Gastroenterology, Nutrition, and Liver Diseases, Schneider Children's Medical Center of Israel, Petah Tikva, Israel

[6]KidZ Health Castle, UZ Brussel, Vrije Universiteit Brussel, Brussels, Belgium

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MEMBERS OF THE ESPGHAN SPECIAL INTEREST GROUP ON GUT MICROBIOTA AND MODIFICATIONS

Berni Canani, Roberto; Campoy, Cristina; Domellöf, Magnus; Dinleyici, Ener Cagri; Francavilla, Ruggiero; Gutiérrez-Castrellón, Pedro; Guarino, Alfredo; Haiden, Nadja; Hojsak, Iva; Indrio, Flavia; Mihatsch, Walter; Mosca, Alex; Orel, Rok; Salvatore, Silvia; Savino, Francesco; Shamir, Raanan; Szajewska, Hania; Vandenplas, Yvan; Van den Akker, Chris H.P; Van Goudoever, Johannes B.; Weizman, Zvi.

CONFLICT OF INTEREST STATEMENT

Hania Szajewska: serves as a board member of the International Scientific Association for Probiotics and Prebiotics (ISAPP), a role which is unpaid and voluntary. She has participated as a clinical investigator, advisory board member, consultant, and speaker for several companies, including Arla, BioGaia, Biocodex, Danone, Dicofarm, Nestlé, NNI, Nutricia, Mead Johnson, and Novalac. Ener Cagri Dinleyici has participated as a clinical investigator, advisory board member, consultant, and speaker for BioGaia, Biocodex, Nestle Health Science, Nestle Nutrition Institute and Nutricia. Alfredo Guarino has received research grant by IPSEN, Biocodex and Dicofarm. Alexis Mosca: Advisory board member, consultant, and speaker for several companies, including BioGaia, Biocodex, Danone (Nutricia), Nestlé, Havea, PiLeJe, Sodilac, Mead Johnson, Adare (Dsm-Firmenich). Raanan Shamir: participated as a clinical investigator, and/or advisory board member, and/or consultant, and/or speaker for Abbott Nutrition, Danone, ELSE Nutrition, Nestle Health Science, Nestle Nutrition Institute, Nutricia. Yvan Vandenplas: participated as a clinical investigator, and/or advisory board member, and/or consultant, and/or speaker for Abbott Nutrition, Alba Health, Arla, Biogaia, Danone, ELSE Nutrition, Friesland Campina, Nestle Health Science, Nestle Nutrition Institute, Nutricia, Pileje, United Pharmaceuticals (Novalac).

ORCID

Yvan Vandenplas https://orcid.org/0000-0002-1862-8651

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