START CENTER
STRATEGIC ANALYSIS,
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EED INTERVENTIONS: PRE- AND PRO-BIOTIC SAFETY

UNIVERSITY OF WASHINGTON STRATEGIC ANALYSIS, RESEARCH, & TRAINING (START) CENTER

DELIVERABLE FOR THE BILL AND MELINDA GATES FOUNDATION

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ABBREVIATIONS

Study Methods/Analysis:

PP - Per Protocol
ITT - Intention to treat
RCT - Randomized Control Trial

Intervention:

Pre - Prebiotic intervention
Pro - Probiotic intervention
Ctl - Control
Syn – Synbiotic

Results:

NS - Non-significant/No significant/No statistical significance
NR - Not reported

Maternal & Child Health:

IF - Infant formula
BF - Breastfeeding/Breastfed
LBW - Low birthweight

Author, Year-Title	Hosni et al, 2012 Probiotics-Supplemented feeding in extremely low-birth-weight infants
Location	US
n intervention | N study	50 | 101
Length of TX	Until 34 PMA
Follow-up	Weight and feeding until 28 days (during Tx); Weight until 34 weeks PMA
Loss to Follow-Up	NR (discharge was possible)
Ages	≤ 14 days of age at time of feeding initiation GA (weeks - mean±SD) 25.7±1.4
Probiotic (Genus species) or prebiotic	Probiotic: *Lactobacillus rhamnosus GG LGG* *Bifidobacterium infantis*
Dose	Pro: LGG- 500 million CFU + Bif. - 500 million CFU suspended in 0.5 ml of infants milk Enteral feeding - daily until discharge or 34 weeks postmenstrual age (PMA) Ctl: unsupplemented milk Total parental nutrition was given to all infants until oral nutrition was tolerated at a volume of 100–120 ml kg^-11 per day
Indication	Extremely low-birth-weight infants "feeding tolerance"
Growth/Development Results	Percentage of infants with weight below the 10th percentile at 34 weeks PMA Pro: 58% Ctl: 60% (p=0.83) t=28 days after feeding initiation Parental fluid intake NS Daily weight gain (mean±SD) Pro: 14.3 ± 7.4 g Ctl: 11.8 ± 4.8 (p=0.06) Growth velocity Pro: 14.9 ± 6.5 g/day Ctl: 12.6 ± 4.5 g/day (p=0.05)
Bacteremia - other	NS differences in incidence of sepsis No sepsis detected related to probiotic organisms
Infection	NS differences in incidence of NEC

Serious Adverse Events	Mortality was not different between the two groups RR=0.77, 95% CI(0.18, 3.25) NS differences in respiratory support required (conventional/high frequency ventilation, NCPAP or Nasal Cannula), medication use (methylxanthines, postnatal steroids and PPI/H2 blockers), or central venous line days between the two groups "NS differences in severe intra-ventricular hemorrhage and chronic lung disease"
Other Adverse Events	No report or any adverse or significant event related to probiotic supplement was reported Trend for higher incidence of focal GI perforation periventricular leukomalcia and severe retinopathy in the Pro vs. Ctl group but NS differences
Tolerability	t=28 days after feeding initiation Average daily volume of feeding (mL kg^-1) higher in the Ctl group than the Pro group (Fig. 2) Total parental fluids intakes (mean ± SD) NS differences; Pro: 2069±837 Ctl: 1776±945
Intolerance/AE Drop Outs	NR
Microbiotia Composition	NR

Author, Year-Title	Ben et al, 2008 Low level of galacto-oligosaccharide in infant formula stimulates growth of intestinal *Bifidobacteria* and *Lactobacilli*	
Location	China	
n intervention | N study	Pre (IF): 37 Pre (IF & human milk): 58	164 (with fecal analyses)
Length of TX	3 months	
Follow-up	End of 3 months tx	
Loss to Follow-Up	50% for fecal analyses due to refusal or failure to take fresh sample	
Ages	Range in groups: 38.7-39.4 weeks	
Probiotic (Genus species) or prebiotic	Prebiotic: Galacto-oligosaccharide (GOS)	
Dose	Pre (GOS): 0.24 g/100 mL formula (non-breastfed and breastfed) Ctl: no GOS formula (non-breastfed and breastfed)	
Indication	None	
Growth/Development Results	Length gain during study period (cm/wk) - 3 month follow-up (mean±SD): *p-value = 0.13* GOS formula: 0.95±0.11 GOS + breast milk: 1.01±0.11 Ctl formula: 0.96±0.11 Ctl breastmilk: 0.93±0.10 Weight gain during study period (g/d): *p-value = 0.21* GOS formula: 41.26±5.22 GOS + breast milk: 43.35±4.87 Ctl formula: 40.59±3.95 Ctl breastmilk: 40.97±5.06	
Bacteremia - other	NR	
Infection	NR	
Serious Adverse Events	NR	
Other Adverse Events	NS differences in crying	

Tolerability	Stool consistency *p=0.02* Pre (GOS formula): 2.46±0.62 Pre (GOS formula+human milk): 2.55±0.66 Ctl (human milk): 2.37±0.83 Ctl (formula): 3.11±0.34 NS differences in regurgitation and vomiting between the groups "The frequency of stools was shorter and the stools became softer[GOS group], as seen in breast milk-fed infants"
Intolerance/AE Drop Outs	NR
Microbiotia Composition	All amounts in mean±SD Log10 CFU/g wet faeces *Bifidobacteria* - p=0.01 Pre (GOS formula): 9.01±1.18 Pre (GOS formula+human milk): 8.97±0.85 Ctl (human milk): 9.25±0.93 Ctl (formula): 8.16±0.99 *Lactobacilli* - p=0.03 Pre (GOS formula): 5.91±1.61 Pre (GOS formula+human milk): 5.99±2.12 Ctl (human milk): 5.45±2.16 Ctl (formula): 4.27±2.02 *E. coli* - p=0.67 Pre (GOS formula): 6.35±1.59 Pre (GOS formula+human milk): 5.90±1.84 Ctl (human milk): 5.74±1.68 Ctl (formula): 5.68±2.11 "GOS could stimulate the growth of Bifidobacteria and Lactobacilli as in breastfed counterparts, decrease fecal pH, and increase the production of intestinal SCFA.

Author, Year-Title	Burks et al, 2015 Synbiotics-supplemented amino acid-based formula supports adequate growth in cow's milk allergic infants
Location	US
n intervention | N study	54 | 110
Length of TX	16 weeks
Follow-up	Through tx w/anthropometric measures at 0, 2, 4, 8, 12, and 16 weeks
Loss to Follow-Up	1 from each group Completers in each group Syn: n=43 Ctl: n=47
Ages	Range in groups: 0.6-8.9 months Median: 4.4 months
Probiotic (Genus species) or prebiotic	Prebiotic: Chicory-derived neutral oligofructose, long-chain inulin; and a food-grade pectin-derived acidic oligosaccharide (pAOS) Probiotic: *Bifidobacterium breve*
Dose	Amino acid-based formula (AAF) with synbiotic: Pre: 8 g/l (6.8 g/l oligofructose:inulin 9:1 and 1.2 g/l pAOS Pro: 1.47 X 10^9 CFU/100 ml formula *B. breve*
Indication	Cow's milk allergy (CMA)
Growth/Development Results	(Syn vs.Ctl) during study period (@16wks, Z scores) Length gain difference -0.299, 90% CI (-0.69, 0.09); *p=0.21* LAZ: "Not significantly different between the groups" Weight gain difference during study period (@16 wks, Z scores): 0.147 90% CI (-0.10, 0.39); p=0.32 Head circumference 0.152 90% CI (-0.15, 0.45); p=0.40
Bacteremia - other	NR

Infection	Infection: *p-value = 0.008* Syn: n=1 (2%) Ctl: n=10 (18%) needed 'drugs for functional GI disorders': *p-value = 0.029* Syn: 4% Ctl: 18% needed 'antibacterials for systemic use: *p-value = 0.049* Syn: 17% (amox 9% - p=0.004) Ctl: 32% (amox 32%)
Serious Adverse Events	6 total Syn: 2 events Ctl: 4 events "Investigators determined none due to study formula"
Other Adverse Events	AEs = 81(overall NS) Syn: n=43 Ctl: n=38 Diarrhea *p-value = 0.004* Syn: 12 subjects (22%) Ctl: 2 subjects (4%) "Significant differences were found between the study groups regarding haemoglobin, haematocrit, RBC and alkaline phosphatase. However, these and all other values were within reference ranges"
Tolerability	"Intake levels were comparable in both groups" NS differences in flatulence and stool frequency *Post hoc analyses* NS differences in appearance of water content and average consistency Color differed (more preferred color in Syn group) Significant at weeks 0-2, 2-4, 4-12
Intolerance/AE Drop Outs	Syn: SAE n=6 Other reasons n=2 Ctl SAE n=3

Microbiotia Composition	At t= 4 & 16 wks (proportion of faecal samples in the Syn group) - ref Table 3 *bifidobacteria:* Higher ($p < 0.001$) *C. histolyticum:* Lower ($p=0.009$) *E. rectale/C. coccoides:* Lower ($p < 0.001$) *C. lituseburense:* NS differences between groups At t=4 & 16 weeks faecal pH and SCFA - ref Table 3 feacal pH: Syn lower v. Ctl $p < 0.001$ At t=16 weeks acetic acid levels: Syn higher v. Ctl. $p=0.004$ propionic acid levels: Syn lower v. Ctl $p = 0.006$
Additional Notes	allergies decreased with time at all time points in both groups with NS difference (SCORAD as well)

Author, Year-Title	Cekola et al, 2015 - Growth and tolerance of term infants fed formula with probiotic *Lactobacillus reuteri*
Location	US
n intervention | N study	60 | PP: 122
Length of TX	throughout until 112? (NR)
Follow-up	followed until 112 days
Loss to Follow-Up	n=26 Pro: n=16 Ctl: n=10
Ages	14±3 days
Probiotic (Genus species) or prebiotic	Probiotic: *Lactobacillus reuteri* (DSM 17938)
Dose	Pro: 1.0 x 10^6 CFU/g formula *L. reuteri*- same base as control but lower lactose, 30:70 lactose:maltodextrin and no GOS Ctl: formula only-partially hydrolyzed whey protein with DHA, ARA and 2.2 g protein/100kcal. Carbohydrate source was 70:30 lactose:maltodextrin and 4 g/100kcal galacto-oligosaccharides (GOS)
Indication	None
Growth/Development Results	Enrollment to 4 months Length gain: NS differences Some data in Table 4 Weight gain - g/day (mean ± SD): *p-value = 0.66* Pro: 29.6 ± 5.9 Ctl: 30.7 ± 7.2 NS differences in head circumference
Bacteremia - other	NR
Infection	NR
Serious Adverse Events	6 total - hospitalization reported as "unrelated" to the product Pro: 3.6% Ctl: 3.8%

Other Adverse Events	Overall NS difference Pro: 70.2% Ctl: 69.6% <u>Pro: n=59 with 167 AEs</u> "Probable" relationship to product: n=13 Gas: 4 Constipation: 3 Fussiness: 2 Excessive Crying: 1 Apparent Colic: 1 Hematochezia: 1 Gastroesophageal reflux: 1 <u>Ctl: n=55 with 156 AEs</u> "Probable" relationship to product: n=6 Vomiting: 1 Irritability: 1 Gas: 2 Constipation: 2 <u>No vomiting - NS</u> Pro: 80% Ctl: 87%
Tolerability	"Both formulas were well tolerated." NS difference in stool consistency, frequency, color nor in flatulence or spit-up <u>Formula intake</u> NS differences Avg amt of formula consumed by all subjects of 28.32 oz/d
Intolerance/AE Drop Outs	"During the study, it was noted that one group had a lower number of subjects completing the study per the protocol. To deliver 56 completed subjects per group in a timely manner, the last 16 eligible subjects were randomly assigned in a 1:4 ratio in favor of the group with the lower completion rate." SAE n=1 Ctl
Microbiotia Composition	NR

Author, Year-Title	Chouraqui et al, 2008 Assessment of the safety, tolerance, and protective effect against diarrhea of infant formulas containing mixtures of probiotics or probiotics and prebiotics in a randomized controlled trial	
Location	France	
n intervention | N study	PP: 174 Group 1: 60 Group 2: 54 Group 3: 60	ITT: 284 PP - until 4 months: 227
N study		
Length of TX	4 months	
Follow-up	12 months	
Loss to Follow-Up	Total n = 116 Before full 4 month Tx n=31 Between 4 and 12 month endpoint n=85 NS difference between groups	
Ages	Range: *p-value = 0.38* 39.5 ± 1.2 - 39.7 ± 1.3	
Probiotic (Genus species) or prebiotic	Probiotic: *Bifidobacterium longum* (BL999) *Lactobacillus rhamnosus* (LPR) *Lactobacillus paracasei* (ST11) Prebiotic: 90% galacto-oligosaccharide/10% short-chain fructo-oligosaccharide (GOS/SCFOS)	

Dose	Experimental Arms: Ctl formula + **Group 1: BL999 + LPR** BL999: 1.29 X 10^8 CFU/100 mL LPR: 6.45 X 10^8 CFU/100 mL **Group 2: BL999 + LPR + GOS/SCFOS** BL999: 1.29 X 10^8 CFU/100 mL LPR: 6.45 X 10^8 CFU/100 mL GOS/SCFOS: 0.4 g/100 mL **Group 3: BL99 + ST11 + GOS/SCFOS** BL999: 2.58 X 10^8 ST11: 2.58 X 10^8 GOS/SCFOS: 0.4 g/100 mL Ctl: unsupplemented formula (Nan; Nestec SA, Konolfingen, Switzerland)
Indication	None
Growth/Development Results	NS difference in mean length, weight gain, or head circumference between the formula groups and the control groups at 4 months "In those that completed 12 months z-scores were close to 0 at all times during the study" Sex-disaggregated data available in Table 3
Bacteremia - other	NR
Infection	Observational Period: NS difference in frequency of antibiotic treatment or hospitalization among groups; AE s included infections

Serious Adverse Events	At least 1 SAE in 24 infants Unassessed for probable association with product: n=4 Unrelated to product: n=16 <u>Total number of events by group (details Table 5)</u> Group 1: n=11 (15.7%) Group 2: n=7 (10%) Group 3: n=4 (5.4%) Control: n=7 (10%) <u>Probably related to product</u> Group 1: Cow's milk allergy: n=2 (Group 1) Control: Diarrhea: n=1 Gastroesophageal reflux disease: n=1
Other Adverse Events	At least 1 AE in 184 infants "78% of AEs were respiratory and GI problems (including allergies) and infections"
Tolerability	Treatment period: Diarrheal incidence: *NS difference btwn groups* **Stool frequency:** Group 2 vs. Ctl: 2.1/day vs. 1.6/day p=0.03 **Liquid stoolS (OR):** **Group 3 vs. Ctl & vs. Group 1:** 3.17 p=0.005, and 2.29 p=0.008 respectively Frequency of other stool consistencies, flatulence, colic, spitting up, and vomiting, NS difference. Observational period: Diarrheal incidence: Group 1 vs. Ctl: 5/37 vs. 13/30; p=0.03
Intolerance/AE Drop Outs	Withdrawals not including LTFU <u>Formula change</u> Group 1: n=7 Group 2: n=5 Group 3: n=4 Ctl: n=5 <u>AEs</u> Group 1: n=1 Group 2: n=1 Group 3: n=1 Clt: n=2

Microbiotia Composition	NR
Additional Notes	"Although not statistically significant, the differences in z-scores for length at 12 mo suggest that there might be a difference in the effect of the 2 formulas containing LPR compared with the control. "

Author, Year-Title	Closa-Monasterolo et al, 2013 Safety and efficacy of inulin and oligofructose supplementation in infant formula: Results from a randomized clinical trial
Location	Spain
n intervention | N study	128 | 252
Length of TX	until 4 months old (+/- 5 days)
Follow-up	at t=4 months
Loss to Follow-Up	n=11
Ages	Neonates; Range of means: 39.8±1.3-39.9±1.3 gestational weeks
Probiotic (Genus species) or prebiotic	Prebiotic: Oligofructose and long-chain inulin (50:50) known as Orafti!Synergy1 (SYN1)
Dose	Pre: 0.8 g/dl Ctl: supplemented with an amount of maltodextrin equivalent to SYN1-supplemented formula
Indication	None
Growth/Development Results	NS differences between groups at any time points: weight, length, head, waist and arm circumference or tricipital and sub-scapular skinfold results
Bacteremia - other	NR
Infection	NR
Serious Adverse Events	NR Urine and blood serum parameters were collected with experimental and control groups demonstrating similar levels (ref: Table 5)
Other Adverse Events	n=67 events frequent vomiting, regurgitation or digestive discomfort, skin rash, bloody stools, and lack of weight gain - NS difference loose stools: 2% SYN1 vs. 8 % p <0.05 Regurgitation and digestive discomfort (n/day) *NS differences* Time crying (min/day) at month 4 *p<0.05* SYN1: 20 Ctl: 15
Tolerability	"SYN-1 supplementation is safe in terms of infant ingestion" "The infant formula had no effect on the subjects' reasons for dropping out of the study. The digestive symptoms (e.g., regurgitation or gastrointestinal symptoms) reported as reasons for withdrawal were those that are characteristic of this period of infancy (for both formula and breastfed infants)."

Intolerance/AE Drop Outs	Symptoms - includes all infants who abandoned the study to switch to another infant formula due to digestive symptoms Subjective - includes parents' subjective perceptions of formula acceptance <u>Totaled from Fig 1</u> Symptoms SYN1:n=22 Ctl: n=19 Subjective SYN1:n=8 Ctl: n=11
Microbiotia Composition	<u>Linear regression analyses with two covariates (i.e., formula and bacterial strain)</u> *Bifidobacterium:* direct association with SYN1 and fecal consistency score (13.5% of variability explained) $p<0.05$ *Enterobacteriaceae:* inverse association with SYN1, bacteria counts with stools frequency ($p<0.001$) Ref Table 2 for more analyses

Author, Year-Title	Fanaro et al, 2008 Galacto-oligosaccharides are Bifidogenic and safe at weaning: a double-blind randomized multicenter study
Location	Italy Spain
n intervention | N study	77 | 159
Length of TX	18 weeks
Follow-up	Through 18 wk tx period; baseline, 6 weeks and 18 weeks
Loss to Follow-Up	n=9 Pre: n=4 Ctl: n=5
Ages	4-6 months
Probiotic (Genus species) or prebiotic	Prebiotic: Galacto-oligosaccharide (GOS)
Dose	As part of formula Pre: 5 g/L GOS Ctl: 5 g/L extra maltodextrin in place of GOS -milk volumes at least 230 mL/day which is = 1.15 g GOS
Indication	None; non-breastfeeding infants
Growth/Development Results	NS differences between the groups or subgroups: Weights, length at timepoints: birth, baseline, week 6, or week 18
Bacteremia - other	NR
Infection	NR
Serious Adverse Events	NR
Other Adverse Events	"None of the infants fed the supplemented follow-on formula had watery stools on average (maximum score 4.2) at any time during the observation period"
Tolerability	NS differences in the incidence of crying, regurgitation, vomiting, and flatulence Subgroup of 88 in Italian centers **Stool frequency (arbitrary units AU ± SD):** *p<0.001* Pre (GOS): 2.78 ± 0.45 Ctl: 2.25 ± 0.58 Another subgroup of n=52 NS difference in urinary osmolarity
Intolerance/AE Drop Outs	Formula changes and reasons Pre (GOS): n=0 Ctl: n=5 (1 gastroesophageal reflux, 1 enteritis, 3 constipation) Antibiotic therapy withdrawals Pre (GOS): n=13 Clt: n=8

Microbiotia Composition	*Bifidobacteria* - medians log10 CFU(25%Q–75%Q) t = 6 weeks, p=0.012 Pre (GOS): 9.96 (9.21–10.53) Ctl: 9.64 (8.82–9.96) t = 18 weeks, p=0.027 Pre (GOS): 9.86 (8.99–10.18) Ctl: 9.38 (8.35–9.90) Fecal Numbers of *lactobacilli*, *Bacteroides*, *clostridia*, and *Enterobacteriaceae* t=6 weeks or t=18 weeks NS differences between the groups

Author, Year-Title	Firmansyah et al, 2011 Improved growth of toddlers fed a milk containing synbiotics
Location	Indonesia
n intervention | N study	ITT: 199 | ITT: 393
Length of TX	4 months
Follow-up	Every 2 months for 1 year (until 24 months of age)
Loss to Follow-Up	Syn: n= 47 Ctl: n=34
Ages	12 months
Probiotic (Genus species) or prebiotic	Probiotic: *Bfidobacterium longum* (BL999) *Lactobacillus rhamnosus* (LPR) Prebiotic: Inulin Fructo-oligosaccharide LCPUFA: Arachidonic acid (AA) docosahexaenoic acid (DHA)
Dose	Per 100 g of study formula Synbiotic: Pro: 1 X 10^7 CFU/g BL999 2 X 10^7 CFU/g LPR Pre: 1.02 g Inulin 2.38 g Fructo-oligosaccharide AA: 24 mg DHA: 23 mg Ctl: ref: table 1 for standard formula ingredients
Indication	None

Growth/Development Results	Length NS differences (values NR) in length gain between the two groups *16 months (mean ± SD)* Syn: 77.8 ± 3.0 cm Ctl: 77.9 ± 3.4 cm Change in WAZ - ITT (12 to 16 months) p=0.04 Syn: 0.11 ± 0.40 Ctl: 0.02 ± 0.40 Head circumference NS differences *16 months (mean ± SD) cm* Syn:45.7 ± 1.33 Ctl: 45.6 ± 1.51
Bacteremia - other	NR
Infection	NR
Serious Adverse Events	n=6; Unrelated to study formulas Syn: n=2, typhoid and typhoid+dengue Ctl: n=4, typhoid, febrile seizures, fever/diarrhea/dehydration, fever/icertic/alcoholic stool/hepatitis
Other Adverse Events	"Most toddlers experienced at least one AE during the study [Syn v. Ctl] 94.5% vs. 94.9%" Syn: n=199 Ctl: n=194 Risk of diarrhea (RR) - parental assessment Syn to Ctl: - 1.25, p=0.03 Syn: 110 (55.3%) Ctl: 86 (44.3%) Others listed with NS differences: rhinitis, upper RTI, fever, coughing, stomatitis, conjunctivitis, vomiting, furunculosis, dermatitis (see Table 6 for ref)
Tolerability	NS differences in stool frequency or any stool characteristics between the two groups at 16 months Stool hematest was negative in >90% of toddlers in both groups "Both milks were tolerated well and there were no safety issues identified"
Intolerance/AE Drop Outs	Adverse events Syn: n=6 Ctl: n=2

Microbiotia Composition	All changes in the 12 month to 16 month period (ages - study follow-up at 4 months More details ref Table 4 *lactobacilli/enterococci* Syn v Ctl: Increase in [change in] counts (0.023) and proportion (0.037) *bactobacilli/enterococci* NS differences *Bifidobacteria* Syn: NS differences between visits (in change); slight decrease in this group however *clostridia/ eubacteria* Increase in counts in both groups, and increase in proportion between 12 and 16 months in both groups but NS between them

Author, Year-Title	Gibson et al, 2009 Safety of supplementing infant formula with long-chain polyunsaturated fatty acids and *Bifidobacterium lactis* in term infants: a randomised controlled trial
Location	Australia
n intervention | N study	72 | 142
Length of TX	~7 months (enrollment until age)
Follow-up	Until 7 months of age Visits approximately at 14, 28, 42, 56, 91, 119, 182, and 212 days
Loss to Follow-Up	n=3 Pro: n=1 Ctl: n=2
Ages	Newborn
Probiotic (Genus species) or prebiotic	Probiotic: *Bifidobacterium lactis* LCPUFA: Arachidonic acid (AA)
Dose	*Intervention* Pro: 3.85 X 10^8 CFU/kcal LCPUFA (percentage of total fatty acids) AA: 0.24 DHA: 0.24 *Control* Same formula (ref: Table 1) without probiotic, LCPUFA or EPA
Indication	None - birth weight between 2500 and 4500 g
Growth/Development Results	Mean change length (mm/month) in PP: mean (SD) *NS difference* Pro: (n=27) female 32.8 (4) (n=24) male 35 (3.7) Ctl: (n=23) female 32 (4.6) (n=19) male 37.3 (4.9) Weight gain PP mean: *NS difference* 2.0 g/day 90% CI (0.1-3.8 g/day) "A comparison of weight-for-age, length-for-age and head circumference-for-age with the CDC growth references showed that z-scores were within the normal ranges for both groups"
Bacteremia - other	NR

Infection	Intestinal infectious disease *NS differences* Pro: n=29 Ctl: n=41 Respiratory infections Pro: n=65 Ctl: n=70 antibody titres related to vaccines reported below Day 212 No differences between groups in mean titres for antibodies for: diphtheria *H. influencae* type b hepatitis B pertussis filamentous haemagglutinin pertussis pertactin pertussis toxin tetanus
Serious Adverse Events	n=40 events in n=29 infants "37 considered unrelated or unlikely to be related to formulas" Pro: n=18 infants Ctl: n=11 infants No deaths though all required hospitalization Respiratory problems Pro: n=7 Ctl: n=4 Gastrointestinal problems Pro: n=3 Ctl: n=3 Probably related to formulas Pro: 1 gastrointestinal problem Ctl: 1 gastrointestinal problem, 1 respiratory problem

Other Adverse Events	n=403 events in n=124 infants *p=0.21* Pro: n=60 infants Ctl: n=64 infants Frequency of feeding problems (vomiting during or right after feeding: *p = 0.03* Pro: 15 Ctl: 31 Other symptoms with NS difference listed in Table 5: symptoms and signs involving the digestive system Candidiasis Dermatitis
Tolerability	Mean daily volume of formula intake (course of study) PP: *p=0.014* Pro: 893 (130) mL/day Ctl: 830 (134) "Stools, colic, spitting up, vomiting and restlessness occurred at similar frequencies in the two groups" "stool characteristics were similar between the two groups" [with the exception of color]
Intolerance/AE Drop Outs	Discontinued intervention Pro: n=9 Ctl: n=6 Parents' perception of constipation/irritability Pro: n=1 Ctl: n=1 No explanation Pro: n=5 Ctl: n=4
Microbiotia Composition	NR
Additional Notes	"None of the standard blood biochemical measurements differed between the two groups (data not shown), except that the measurements of blood glucose and albumin concentrations were higher in the control group (4·7 (SD 0·5) v. 4·4 (SD 0·7) mmol/l, P1⁄40·012 for glucose and 40·8 (SD 2·5) v. 39·5 (S D 2·9) g/l, P1⁄4 0·03 for albumin)" - all normal range

Author, Year-Title	Gil-Campos et al, 2012 *Lactobacillus fermentum* CECT 5716 is safe and well tolerated in infants of 1–6 months of age: a randomized controlled trial
Location	Spain
n intervention | N study	66 | 137
Length of TX	~5 months (until 6 months of age)
Follow-up	~5 months (until 6 months of age)
Loss to Follow-Up	Syn: n=0 (but 2 did not attend visits Ctl: n=1 (but 8 did not attend visits)
Ages	1 month
Probiotic (Genus species) or prebiotic	Probiotic: *Lactobacillus fermentum* CECT5716 Prebiotic (both groups) Galacto-oligosaccharides (GOS)
Dose	Pro: 10^7 CFU/g *L. fermentum* Intervention and Ctl groups Pre: 0.3 g/100 mL GOS
Indication	None - formula fed
Growth/Development Results	Length **LAZ:** *p=0.021* Syn higher than Ctl w/ Pre (curves shown in Fig. 3) **Length gain (cm/day):** *NS differences* Syn: 0.96 ± 0.3 Ctl w/ Pre: 0.90 ± 0.2 **Length at 6 month visit:** *p = 0.038* Syn higher than Ctl w/ Pre NS differences between groups in weight or head circumference
Bacteremia - other	NR
Infection	GI Infection: *p=0.018* IRR Syn: Ctl(w/Pre) - 0.289 (0.085, 0.831) Syn: n=5 Ctl w/Pre: n=17 Respiratory Infection: *NS differences* IRR Syn: Ctl(w/Pre) - 0.977 (0.623, 1.530) Antibiotic Tx:

	NS differences IRR Syn:Ctl (w/Pre) - 1.105 (0.362, 3.702) Syn: n=8 Ctl w/Pre: n=7 Total infections n=63 *NS differences;* Febrile episodes n=13 *NS differences* (ref Table 4)
Serious Adverse Events	NR
Other Adverse Events	"No adverse effects associated to probiotic supplementation were detected during the study"
Tolerability	Daily intake of formula: *NS differences* Syn(w/Pre): 587.8 ± 201.3 mL/day Ctl: 630.9 ± 197.7 mL/day Feeding-related behavior *Similar in both groups (ref Table 3)* (fecal depositions/day, feces color, consistency, flatulence, regurgitation, sleeping hours and behavior)
Intolerance/AE Drop Outs	NS differences in drop out rates between the two groups Change of formula due to reflux Syn: n=2 Ctl: n=2 Consumption of other infant formula Syn: n=1
Microbiotia Composition	*Lactobacilli, Bifidobacteria, Clostridia, Bacteroidaceae* (observed mean of fecal counts at each time point) Similar between groups, although it was observed a significant increase in these bacterial groups with time (Table 5) was observed *L. fermentum* CECT5716 Syn: Alive in fecal samples of 53% of the infants Ctl: n=2 samples alive "The capability of fecal microbiota of infants to produce short chain fatty acids (butyric, propionic and acetic) and concentration of IgA in feces were similar in both groups"

Author, Year-Title	Hays et al, 2015 Probiotics and growth in preterm infants: A randomized controlled trial, PREMAPRO study	
Location	France	
n intervention | N study	147 Group 1: 50 Group 2: 49 Group 3: 48	199
Length of TX	28 days	
Follow-up	~42 days (including Tx period)	
Loss to Follow-Up	n=0 (but other withdrawals)	
Ages	Birth to 7 days	
Probiotic (Genus species) or prebiotic	Probiotic: Group 1: *Bifidobacterium lactic* Group 2: *Bifidobacterium longum* Group 3: *B. lactic* + *B. longum*	
Dose	Each probiotic was 10^9 CFU/d (START note: unclear whether the combination group has this as the total or not) Ctl: maltodextrin alone	
Indication	LBW infants (GA between 25 and 31 weeks, birthweight: 700-1600 g)	
Growth/Development Results	LAZ NS differences between the intervention groups WAZ NS differences between the groups Weight gain p=0.17 Pro (all groups) : 15.9 ± 4.1 g/kg*day Ctl: 16.6 ± 3.1 g/kg*day Head circumference NS differences between the groups *At end of supplementation HC/A z-score (ref Table 3)* Pro (all Groups): -1.25 (-1.68, -0.75) Ctl: -0.97 (-1.41, -0.58)	
Bacteremia - other	Bloodstream infections % of subjects with at least one infection (95% CI): ref: Table 6 for individual groups *NS difference between the groups (p=0.912)* **Coagulase-negative staphylococci:** Pro (all Groups): 56 (37, 76) Ctl: 80 (55, 100)	

	Staphylococcus aureus: Pro (all Groups): 28 (10, 46) Ctl: 0 (0,0) ***Candida spp.:*** Pro (all Groups): 0 (0,0) Ctl: 10 (0, 29) **Other:** Pro (all Groups): 16 (2, 30) Ctl: 10 (0, 28)	
Infection	Antibiotics *NS difference between the groups* Group 1: n= 8 (16%) Group 2: n= 3 (6.3%) Group 3: n = 9 (19.1%) Ctl: n = 6 (11.5%) NEC Pro (all Groups): n=8 (5.5%) Ctl: n=3 (5.8%)	
Serious Adverse Events	n= 13, P: n=2; C n=11 "None of these SAEs were considered to be related to study treatment" **Mortality:** P (all Groups): n=5 C: n=1	
Other Adverse Events	n=60 events; n = 45 subjects P (all groups): 35 (24%) infants, 45 events C: 10 (19.2%) infants, 15 events Possibly related adverse events P (all groups): n=5 (3.4%) C: n=1 (19%)	
Tolerability	Mean Gastrointestinal tolerance score P (all Groups): 1.03 ± 0.39 C: 1.05 ± 0.36 *Poor gastrointestinal tolerance duration was similar between the two groups, p=0.21 (days)* Mean age full enteral feeding *p = 0.67* P (all Groups): 16.6 ± 9.7 days C: 15.8 ± 9.3 days	
Intolerance/AE Drop Outs	Parent's decision Pro (all Groups): n = 1	Adverse Event Pro (all Groups): n = 10

	Ctl: n = 1 Introduction of another formula Pro (all Groups): n = 7 Ctl: n = 2	Ctl: n = 4
Microbiotia Composition	At t= 3wks of Tx: Most frequently detected families in stool in decreasing frequency NS differences between groups *Staphylococcus spp.* *Clostridiales* *Enterobacteriaceae* *Enterococcus spp*. Mean diversity scores - p = 0.75 Pro (all Groups): 3.4 ± 1.3 Ctl: 3.4 ± 1.8 *Bifidobacterium spp*. - p=0.04 Pro (all Groups): 30.1% Ctl: 13.0% Particularly in infants in specific groups *B. lactis along* (34.8%) - p=0.03 *B. longum* (32.6%) - p=0.04 (ref Table 5)	

Author, Year-Title	Kukkonen et al, 2008 Long-term safety and impact on infection rates of postnatal probiotic and prebiotic (synbiotic) treatment: randomized, double-blind, placebo-controlled trial
Location	Finland
n intervention | N study	ITT: 468; 506 | ITT: 1223 mothers; 939 infants
Length of TX	(Mothers 4 weeks before delivery) 6 months after birth
Follow-up	Through 24 months (including Tx) with visits or questionnaires at ages 3, 6, 12, and 24 months
Loss to Follow-Up	NR
Ages	Pregnant mothers and infants at birth
Probiotic (Genus species) or prebiotic	Probiotic: *Lactobacillus rhamnosus* GG and LC705 *Bifidobacterium breve* (Bb99) *Propionibacterium freudenreichii* spp *shermanii* JS Prebiotic (just infants): Galacto-oligosaccharide (GOS)
Dose	Synbiotic (Syn) Pro (mix of all): 8-9 X 10^9 CFU/capsule (broken and mixed for infants in liquid (breastmilk, water, or formula) Pre: 0.8 g GOS
Indication	pregnant mothers carrying infants at high risk for allergy
Growth/Development Results	LAZ Similar between two groups **6 month measurement:** Syn: 0.00 ± 0.97 Ctl: -0.04 ± 0.98 **24 month measurement:** Syn: 0.28 ± 1.01 Ctl: 0.34 ± 0.96 Weight Similar between groups, reporting 6 month only (ref: Table 3) Syn: 8.16 kg ± 0.98 Ctl: 8.09 kg ± 0.95 Head circumference (mean±SD) Reporting 6 month only (ref: Table 3) Syn: 43.9±1.3 Ctl: 43.9±1.3

Bacteremia - other	Sepsis Syn: n=6 Ctl: n=6
Infection	All reported during the treatment period; there were some differences in 6-24 month follow-up favoring Syn - pg. 10 for details Antibiotics OR: 0.74 95% CI (0.55-1.00) *p=0.049* Syn: 23% Ctl: 28% *NS differences between the groups* Gastroenteritis Syn: 13% Ctl: 14% Respiratory Infections Syn: 66% Ctl: 68% Middle Ear Infections Syn: 15% Ctl: 19%
Serious Adverse Events	Hospitalization 0-2 years (baseline to follow-up including time after Tx) - includes sepsis numbers Syn: n=25 Ctl: n=37
Other Adverse Events	"NS differences in parent-re- ported neonatal morbidity of any cause for infants in the synbiotic group, compared with those in the placebo group" Less-frequent crying 10% in each group

Tolerability	Difficulties swallowing the powder n=6 infants (1 choking event recovered) "Feeding-related behaviors (vomiting, constipation, ex- cessive crying, and abdominal discomfort) occurred similarly in the study groups" <u>Colic (crying >=4 hours per day for >= 3 days/wk)</u> Similar between both groups 4% <u>Defecating >=3 times/day</u> p<0.001 Syn: 18% Ctl: 29%
Intolerance/AE Drop Outs	<u>Abdominal discomfort</u> Syn: n = 26 Ctl: n = 28 <u>Vomiting</u> Syn: n = 4 Ctl: n = 7 <u>Crying</u> Syn: n = 2 Ctl: n = 1 Ref: Table 2 for full breakdown of discontinuation symptoms
Microbiotia Composition	NR

Author, Year-Title	López-Velázquez, 2013 Safety of a dual potential prebiotic system from Mexican agave "Metlin® and Metlos®", incorporated to an infant formula for term newborn babies: a randomized controlled trial	
Location	Mexico	
n intervention | N study	Group 1 (Syn): 93 Group 2 (Syn): 93 Group 3 (Syn): 89 Group 4 (Pro): 89 *Group 5 (IF): 89* *Group 6: human milk: 147*	ITT: 600
Length of TX	6 months	
Follow-up	Every month for 6 months 66,120 days of monitoring 66,200 days of follow-up (Eczema assessment)	
Loss to Follow-Up	NR	
Ages	≤ 27 days	
Probiotic (Genus species) or prebiotic	Probiotic: *Lactobacillus* GG (LGG) Prebiotic: Melitin and Metlos TM:agave fructans (fructo-oligosaccharides)	
Dose	*Ad libitum as only nutritional source until 4th visit after which no restrictions on complementary feeding* Group 1: 0.2g Meltin, 0.3g Metlos, & 0.3g LGG Group 2: 0.5g Meltin & 0.3g LGG Group 3: 0.5g Metlos & 0.3g LGG Group 4: 0.3g LGG	
Indication	None	
Growth/Development Results	No difference observed between groups in weight, height, MUAC, and skinfold thickness Pro + Metlin + Metlos Weight: 3070 ± 650 Height: 49.7 ± 2.27 MAC: 9.8 ± 0.95 Human Milk: Weight: 3,250 ± 460 Height: 50.3 ± 2.06 MAC: 9.9 ± 1.07	
Bacteremia - other	NR	
Infection	NR	
Serious Adverse Events	NR	

Other Adverse Events	Stool frequency No significant differences Pro + Metlin + Metlos 3.6 ± 2.0/day Human Milk: 3.8 ± 2.4 evacuations/day Stool Consistency Similar in Human milk and Pro + Metlin + Metlos Eczema No significant differences Human Milk: 9.9% Pro + Metlin + Metlos 7.9%
Tolerability	GI intolerance: Lowest frequency of Colic, Abdominal distension, > 10 flatulence episodes/day, and > 10 regurgitations/day among Human Milk and Pro + Metlin + Metlos groups with NS difference between these
Intolerance/AE Drop Outs	NR
Microbiotia Composition	NR

Author, Year-Title	Maldonado et al, 2010 Study and tolerance of the human milk probiotic strain Lactobacillus salivarius CECT5713 in 6-month-old children
Location	Spain
n intervention | N study	40 | 80
Length of TX	6 months
Follow-up	3 months and 6 months
Loss to Follow-Up	none
Ages	6 months
Probiotic (Genus species) or prebiotic	Probiotic: *Lactobacillus salivarius* CECT5713
Dose	Pro: 2X10^6 colony-forming units [CFU]/g *L. salivarius* CECT5713 + Formula
Indication	None
Growth/Development Results	NS difference between groups Pre: Weight: 10 341 ± 1391 g Length: 75.0 ± 2.8 cm Head circumference: 47.6 ± 1.2 cm Ctl: Weight: 9895 ± 1134 g Length: 74.6 ± 2.4 cm Head circumference: 47.1 ± 1.3 cm
Bacteremia - other ***only 1 study reported on probiotic measures**	NR
Infection	Respiratory infections (episodes) *Significantly lower - p<0.05* Pro: n=53 Ctl: n=36
Serious Adverse Events	NR
Other Adverse Events	Episodes of diarrhea *Significantly lower - p<0.05* Pro: n=26 Ctl: n=7
Tolerability	NS significant differences in the digestive tolerance or behavioral characteristics between groups (spitting up, night awakenings, Irritability, severe crying, constipation, daily formula intake (mL), and daily depositions)
Intolerance/AE Drop Outs	No reported drop outs or any AEs related to consumption of the formulas tested

Microbiotia Composition	Fecal content *Lactobacilli* Ctl: Significant decline in concentration from baseline-6 months (8.2 ± 0.1 vs 7.6 ± 0.2 log CFU/g, P < 0.05) Pro: Significantly different from control at 6 months (7.9 ± 0.1 log CFU/g, P < 0.05) *Bifidobacteria:* NS difference *Enterobacteria* Significant decline in concentration from baseline-6 months Ctl: 6.2 ± 0.2 vs 4.8 ± 0.2 log CFU/g, p < 0.05 Pro: 5.2 ± 0.2 log CFU/g, p < 0.05 *Clostridia* Significant decline in concentration from baseline-6 months Ctl: 7.8 ± 0.1 vs 7.1 ± 0.2 log CFU/g, p < 0.05 Pro:7.8 ± 0.2 vs 7.3 ± 0.1 log CFU/g, p < 0.05 *Bacteroides* Pro: Significant decline in concentration from baseline-6 months (7.8 ± 0.1 vs 7.3 ± 0.1 log CFU/g, p < 0.05) *Total aerobes* Pro: Significant decline in concentration from baseline-6 months (7.8 ± 0.2 vs 7.5 ± 0.1 log CFU/g, p < 0.05) Significantly different from control at 6 months (7.1 ± 0.2 vs 7.5 ± 0.1 log CFU/g, p < 0.05) *L. salivarius CECT5713* Detected by PCR in the fecal samples of 90% (36 of 40) of pro vs 0 in ctl Short-chain fatty acids content *Acetate and Propionate* NS differences between groups or in the same group throughout trial B*utyrate* Pro: Significant increase at 6 months p < 0.05 Ctl: NS difference from baseline-6 months

Author, Year-Title	Meli et al, 2014 Growth and safety evaluation of infant formulae containing oligosaccharides derived from bovine milk: a randomized, double-blind, noninferiority trial	
Location	Italy	
n intervention | N study	RCT Ctl (IF): 84 BF (ref):30 Pre: 99 Syn: 98 PP Ctl (IF): 57 BF (ref): 12 Pre: 60 Syn: 56	311
N study	311	
Length of TX	4 months	
Follow-up	12 months	
Loss to Follow-Up	Clt (IF): n=1 Pre: n=3 Syn: n=5 BF ref: n=6	
Ages	≤14 days	
Probiotic (Genus species) or prebiotic	Prebiotic: Bovine milk-derived oligosaccharides (galacto-oligosaccharides,3'- and 6'-sialyllactose, and other oligosaccrides from bovine milk) Probiotic: *Bifidobacterium longum* ATCC BAA-999 (Bl999) *+* *Lactobacillus rhamnosus* CGMCC 1.3724 (LPR)	
Dose	Pre (IF+BMOS): 7.3 ± 1.0 g/100 g of oligosaccharide concentration in powder formula (10 g/L in the reconstituted formula) Syn (IF+BMOS+Pro): 7.3 ± 1.0 g/100 g of oligosaccharide concentration + 2X10^7 CFU/g *B. longum +* 2X10^7 CFU/g (LPR)	
Indication	None	
Growth/Development Results	Weight gain, g/day, mean (SD) Ctl (IF): 30.2 (6.2) Pre (IF+BMOS): 31.5 (6.5) Syn (IF+BMOS+Pro): 30.5 (6.3) Length gain, mm/day, mean (SD)	

	Ctl (IF): 1.07 (0.17) Pre (IF+BMOS): 1.08 (0.19) Syn (IF+BMOS+Pro): 1.06 (0.20) HC gain, mm/day, mean (SD) Ctl (IF): 0.58 (0.10) Pre (IF+BMOS): 0.57 (0.10) Syn (IF+BMOS+Pro): 0.56 (0.09) NS difference between groups mean daily gains of length and head circumference (p>0.05) Mean daily gain of weight between groups <1g/day
Bacteremia - other	NR
Infection	NR
Serious Adverse Events	Not considered related to study formula n= 26 events in 25 infants (Pneumonia, bronchitis, abdominal pain, gastroenteritis, diarrhea, SIDS, UTI, hernia inguinal, convulsions, stupor, gastroesophegeal reflux, aponea, and upper respiratory tract infection)
Other Adverse Events	At least 1 AE n=125 participants NS differences were observed between the control and BMOS groups in caregivers' reports of flatulence, vomiting, spitting up, crying, fussing, and colic Losses to Non-GI AE Pre: n=2 Syn: n=2
Tolerability	GI Tolerability: Caregivers' reports NS difference in reports of regurgitation, vomiting, diarrhea, constipation, and abdominal pain/prolonged crying between groups (p-values ranged 0.19-0.97) Daily stool frequency (Mean ± SD) Ctl: 1.7 ± 0.7 stools/day Pre: 2.6 ± 0.9 stools/day Syn: 2.4 ± 0.8 stools/day Mean difference higher in Pre and Syn groups (p < 0.0001) Stool consistency Ctl infants were more likely to have harder stools than Pre ([OR]: 5.06 [95% CI: 1.33, 19.32], p = 0.0003) or Syn groups (OR: 6.55 [95% CI:1.49, 28.78], p = 0.0001) Investigator-diagnosed colic

	Lower incidence in the Ctl v Pre OR 0.38; 95% CI 0.18, 0.81; p = 0.01 NS difference in incidence comparing Ctl v Syn groups OR 0.56; 95% CI 0.25, 1.24; p = 0.15
Intolerance/AE Drop Outs	<u>Losses to GI intolerance</u> Ctl: 14.3% (n=12) Pre: 17.2% (n=17) Syn: 13.3% (n=13)
Microbiotia Composition	<u>Stool bacterial counts (log10 CFU/g) at age 2 months</u> *Bifidobacteria* Ctl: 8.80 (1.7) Pre: 9.45 (1.8) Syn: 9.87 (1.2) *Lactobacilli* Ctl: 6.13 (0.4) Pro: 6.27 (0.8) Syn: 7.68 (0.7) *Enterobacteria* Ctl: 8.83 (0.9) Pre: 8.61 (0.8) Syn: 8.60 (0.7) *Clostridia* Ctl: 8.49 (1.4) Pro: 6.97 (1.3) Syn: 7.01 (1.3) *Bacteroides* Ctl: 6.37 (0.8) Pro: 6.30 (0.7) Syn: 6.48 (1.2)

Author, Year-Title	Piemontese et al, 2011 Tolerance and safety evaluation in a large cohort of healthy infants fed an innovative prebiotic formula: a randomized controlled trial
Location	Germany
n intervention | N study	414 | 716
Length of TX	12 months
Follow-up	Weeks of age: 8, 16, 24 and 52
Loss to Follow-Up	Withdrawals Pre: n=28 Ctl: n=19 BFref: n=34
Ages	≤8 weeks
Probiotic (Genus species) or prebiotic	Prebiotic: Neutral oligosaccharides and pectin-derived acidic oligosaccharides
Dose	*Primary nutritional source until infants reached 4th months of age, after which no restrictions on complementary feeding* Pro: 6.8 g/L neutral and 1.2 g/L pectin acidic-oligosaccharides +Formula
Indication	None
Growth/Development Results	Mean growth rate (SE) at 16 weeks Pre: 30.9 g/day (0.53) p>0.05 Ctl: 29.9 g/day (0.53) p>0.05 NS difference (Pre v. Ctl) in LAZ, WAZ, and head circumference, skinfold thickness, or MUAC Compared to BF reference LAZ, WAZ and head circumference were lower in prebiotic and control formula fed infants except at 52 weeks Skin fold thicknesses in the breastfeeding group at 8 weeks were larger than prebiotic and control group and smaller at 52 weeks
Bacteremia - other ***only 1 study reported on probiotic measures**	NR
Infection	AEs include some measures of infection Otitis media, bronchitis, gastroenteritis, upper respiratory tract infection, varicella, bronchiolitis, pharyngitis, urinary tract infection
Serious Adverse Events	112 occurring in 110 infants No difference in the incidence of SAEs between formula groups p>0.05 Pre: 10.6% Ctl: 9.4%
Other Adverse Events	640 occurring in 431 infants No difference in the incidence of AEs - p>0.05

	Pre: 31% Ctl: 30% Otitis media, bronchitis, gastroenteritis, upper respiratory tract infection, varicella, bronchiolitis, pharyngitis, urinary tract infection <u>Disease Dropouts</u> Pre: n=7 Ctl: n=6
Tolerability	<u>GI symptoms</u> Spitting, posseting, vomiting, flatulence, cramps, colic, nappy rash No difference in the incidence of any gastrointestinal symptom was detected between the two formula groups (p>.0.05) <u>Stool consistency (pre v. ctl)</u> significantly lower at 8, 16, 24 weeks, and closer to those presented by breastfed infants
Intolerance/AE Drop Outs	<u>Intolerance dropouts</u> Pre: n=10 Ctl: n=7
Microbiotia Composition	NR

Author, Year-Title	Puccio et al, 2007 Clinical evaluation of a new starter formula for infants containing live *Bifidobacterium longum* BL999 and prebiotics	
Location	Italy	
n intervention	Syn: 69; PP 42 Ctl:55	138
N study	138	
Length of TX	7 months	
Follow-up	Days of age 14, 28, 56, 84, and 11	
Loss to Follow-Up		
Ages	<14 days	
Probiotic (Genus species) or prebiotic	Probiotic: *Bifidobacterium longum* BL999 Prebiotic: Galacto-oligosaccharides Fructo-oligosaccharides	
Dose	Synbiotic Pro: 2X10^7 CFU *B. longum* Pre (4 g/L of a mix) : 90% Galacto-oligosaccharides 10% Fructo-oligosaccharides	
Indication	None	
Growth/Development Results	Mean weight gain g/day *Groups were equivalent based on predefined equivalence boundries of 3.9 g/d* ITT population, 0.50, 90% CI (-1.48, 2.48) PP population, 1.09, 90% CI (-0.98, 3.15) Mean changes in recumbent length NS difference between groups p> 0.1 Mean changes head circumference NS difference between groups p> 0.1	
Bacteremia - other	NR	
Infection	AEs include respiratory tract infections	
Serious Adverse Events	Syn: n= 12 Ctl: n=10	

Other Adverse Events	AEs Syn: n= 30 Ctl: n=24 in experimental: Non-serious n= 30 AEs include: Rhinitis, wheezing, cough, respiratory tract infection, diarrhea, constipation, colic, fever, and rash
Tolerability	Stool frequency (occurrences a day) **p=0.018** Syn: 2.2±0.7 Ctl: 1.8±0.9 Stool color: More likely to have yellow stools (OR:1.89, 90% CI 1.21–2.96, p=0.005) Less likely to have green stools (OR:0.51, 90% CI 0.32– 0.81, p=0.004), Less likely to have flatulence (OR:0.6, 90% CI 0.35–1.00, p=0.051) 33% (n=23) attrition in experimental group of which n=18 were due to AEs, no significant difference between groups (p>0.1)
Intolerance/AE Drop Outs	AE dropouts Syn: n= 18 Ctl: n=12 NS difference in the dropout rates between groups (Fisher's exact test, p=0.1) The reasons for dropping out: Life-threatening events (n=5) Hospitalization for 3 days (n=13) High frequency of spitting and crying (n=5) Other adverse events (n =7) No reason provided (n=11)
Microbiotia Composition	NR

Author, Year-Title	Ripoll et al, 2015 scFOS supplemented follow-on formula in healthy infants: Impact on vaccine specific faecal secretory IGA response, faecal bifidobacteria, growth and digestive tolerance
Location	Spain
n intervention | N study	37 | 75
Length of TX	6 months
Follow-up	Months 1, 2, and 6
Loss to Follow-Up	NR
Ages	4 months
Probiotic (Genus species) or prebiotic	Prebiotic: short-chain fructo-oligosaccharides (scFOS)
Dose	Pre: scFOS 3.3/100 g 0.5/100mL at 14% + Milk Formula
Indication	None
Growth/Development Results	NS difference observed (Pre v. Ctl) in changes to weight and height
Bacteremia - other	NR
Infection	81% of infants experienced at least one infectious AE
Serious Adverse Events	Pre: n = 5 infants including bronchitis, bronchiolitis, ear infection, gastroenteritis, inguinal hernia repair, pyelonephritis, and regurgitation, for a mean duration of 3 days over a period of 180 days
Other Adverse Events	NS differences between groups in infants with concomitant treatments (p=0.12) Overall, 81% of infants experienced at least one AE Most prevalent AEs were: nasopharyngitis (28%) bronchitis (12%) gastroenteritis (9%) NS difference in the prevalence or number of AEs between groups (p=0.08)
Tolerability	Vomiting Pre (scFOS group): fewer number of days in (p=0.05) Soft stools Pre (scFOS group): greater number of days (p=0.03) NS differences in regurgitation (p=0.79), constipation (p=0.23), or crying (0.85)
Intolerance/AE Drop Outs	GI intolerance Pre (scFOS) group n=1
Microbiotia Composition	*Bifidobacteria* Significant increase in scFOS group (p=0.03) at 1 month but not at 2 months (p=0.25)

Additional Notes	Duration of the SAEs observed in scFOS group (≥3 days out of 180 days) suggests viral infections that cannot be linked to the prebiotic.	
Author, Year-Title	Saavedra et al, 2004 Long-term consumption of infant formulas containing live probiotic bacteria: tolerance and safety	
Location	US	
n intervention | N study	78 (39/experimental arm) PP High supplement (HS): 39 Low supplement (LS): 40	118
Length of TX	Consumption for total time days(%infants) 114: 25% 192: 50% 268: 75% Aggregate: 24, 830 subject-days	
Follow-up	210 ± 127 days	
Loss to Follow-Up	n=1	
Ages	3–24 months	
Probiotic (Genus species) or prebiotic	Probiotics: *Bifidobacterium lactis* (Bb 12) *Streptococcus thermophilus*	
Dose	Standard milk-based formula + 1 of 2 dosages given ad libitum: Pro: *High Supplement:* 1x10^7 CFU/g each of *B. lactis* & *S. thermophilus* *Low Supplement:* 1x10^6 CFU/g each of *B. lactis* & *S. thermophilus*	
Indication	None	

Growth/Development Results	Growth occurred in all groups (positive z score change), NS differences WAZ HAZ and WLZ between groups <u>Change in WAZ</u> Pro (HS): 0.09 ± 0.64 Pro (LS): 0.06 ± 0.72 Ctl: 0.16 ± 0.69 <u>Change in HAZ</u> Pro (HS): -0.06 ± 0.44 Pro (LS): -0.09 ± 0.60 Ctl: -0.04 ± 0.59 <u>Change in WLZ</u> Pro (HS): 0.40 ± 0.85 Pro (LS): 0.53 ± 1.10 Ctl: 0.45 ± 0.75
Bacteremia - other	NR
Infection	Use of antibiotics lower in supplement groups (p<0.001)
Serious Adverse Events	NR
Other Adverse Events	Incidence of reporting of colic or irritability was significantly lower in both supplemented groups than in the placebo group p<0.001) NS difference in episodes of loose or watery stools, Episodes of emesis or fever with loose or watery stools, Discomfort with bowel movement, Health care attention for illness, Daycare absenteeism due to illness
Tolerability	NR
Intolerance/AE Drop Outs	Three participants withdrew due to parents' perceived effect of formula consumption. <u>HS group</u> Rash n=1 diagnosed to be viral) Loose/watery stool n=1 Loose/watery stool and vomiting n=1
Microbiotia Composition	<u>Mean cumulative bacterial load</u> LS: 9.7x10^7 CFU/kg HS:1.3x10^9 CFU/kg

Author, Year-Title	Vlieger et al, 2009 Tolerance and safety of *Lactobacillus paracasei* ssp. *paracasei* in combination with *Bifidobacterium animalis* ssp. *lactis* in a prebiotic-containing infant formula: a randomised controlled trial	
Location	Netherlands	
n intervention | N study	53 (at 3 months) 41 (at 6 months)	126 first 3 months 80 first 6 months
Length of TX	3 months or 6 months	
Follow-up	6 months	
Loss to Follow-Up	Pro: n=2 Ctl: n=5	
Ages	<7 days	
Probiotic (Genus species) or prebiotic	Probiotic: *Lactobacillus paracasei* ssp. *paracasei* (L. case CRL-431) *Bifidobacterium animalis* ssp. *Lactis* (Bb-12) Prebiotic: galacto-oligosaccharides (GOS)	
Dose	Synbiotic Formula (ad libitum): Pro: 1x10^7 CFU Bb-12/g+ 1x10^7 CFU *L.casei*/g Pre: 0.24 g GOS Ctl: Formula containing 0.24 g GOS	
Indication	None	
Growth/Development Results	NS differences (Pro v. Ctl): Gain in weight (3 months: p=0.64; 6 months: p=0.60) length (3 months: p=0.85; 6 months: p=0.60) head circumference	
Bacteremia - other ***only 1 study reported on probiotic measures**	NR	
Infection	NS significant differences antibiotics, periods with signs of upper respiratory tract infections, and gastrointestinal infections	
Serious Adverse Events	No serious adverse events were reported that could be related to the study formula	
Other Adverse Events	Fewer infants in the probiotics group had developed a rash in the first 3 months (5 v. 12; p=0.05) No other significant difference in the use of visits to their general practitioner, vomiting, diarrhoea, constipation, colic and rash or eczema	

Tolerability	<u>Stool frequency</u> *t=3 months* - p=0.04 Pro: 1.52 Ctl: 1.29 *t= 6 months* - p=0.13 i.e. NS difference between groups <u>Stool consistency</u> Softer stools among probiotic group during the first 3 months (p=0.05) NS difference in stool consistency-scores between 4-6 months (p=0.36)
Intolerance/AE Drop Outs	Intolerance dropouts in syn arm included Colic=6, regurgitation=1, and constipation=3 NS difference between groups
Microbiotia Composition	NR

Author, Year-Title	Weizman et al, 2006 Safety and tolerance of a probiotic formula in early infancy comparing two probiotic agents: a pilot study	
Location	Israel	
n intervention |N study	Pro (Bb-12): 20 Pro (*L. reuteri*): 20	59
Length of TX	4 weeks	
Follow-up	4 weeks	
Loss to Follow-Up	NR	
Ages	3-65 days	
Probiotic (Genus species) or prebiotic	Probiotic: *Lactobacillus reuteri* (ATCC 55730) *Bifidobacterium lactis* (BB-12)	
Dose	One of two in formula: Pro: 1x10^7 CFU/gm or 2.2x10^8 CFU/180ml *L. reuteri* 1x10^7 CFU/gm or 2.2x10^8 CFU/180ml *B. lactis* (BB-12)	
Indication	None	
Growth/Development Results	NS difference: mean weight (p=0.46) length (p=0.69) head circumference percentiles (p=0.59)	
Bacteremia - other	NR	
Infection	Otitis media Ctl: n=1 Upper respiratory infection Pro1: n=1 Pro2: n=1	
Serious Adverse Events	NR	
Other Adverse Events	No adverse effects were noticed throughout the study in all subjects	
Tolerability	Digestive tolerance *NS difference* Stool effort score (p=0.63) Stool consistency (p=0.82) Daily gas score (p=0.67) Daily crying score (p=0.58) Daily crying episodes (p=0.62) Number of night awakenings (p=0.65) Daily restlessness score (p=0.44)	
Intolerance/AE Drop Outs	NR	
Microbiotia Composition	NR	