

Supplementary Table 1. Descriptive statistics and adjusted comparisons of IGSQ-13 score among groups and by visit, FAS

Visit	Group	Geometric means (SD)	Estimate ^a (95% CI)	Group comparisons		
				Comparison	Ratio of estimate (95% CI)	p-value ^b
Baseline	CG	14.7 (1.1)	n/a	n/a	n/a	n/a
	Lo-EG	14.5 (1.1)	n/a	n/a	n/a	n/a
	Hi-EG	14.5 (1.1)	n/a	n/a	n/a	n/a
Visit 2	CG	14.7 (1.1)	14.6 (14.2, 15.1)	--	--	--
	Lo-EG	14.7 (1.1)	14.7 (14.3, 15.1)	Lo-EG vs CG	1.00 (0.96, 1.04)	0.944
	Hi-EG	14.8 (1.2)	14.9 (14.4, 15.3)	Hi-EG vs CG	1.01 (0.97, 1.06)	0.806
Visit 3	CG	14.0 (1.1)	13.9 (13.7, 14.2)	--	--	--
	Lo-EG	13.9 (1.1)	13.9 (13.7, 14.2)	Lo-EG vs CG	1.00 (0.97, 1.03)	0.991
	Hi-EG	13.9 (1.1)	13.9 (13.6, 14.2)	Hi-EG vs CG	1.00 (0.97, 1.03)	0.991

ANCOVA, analysis of covariance; CG, control group (placebo supplement); FAS, full analysis set; IGSQ, Infant Gastrointestinal Symptom Questionnaire (IGSQ); Lo-EG, low-dose *B. infantis*, 1.0×10^8 CFU; Hi-EG, high-dose *B. infantis*, 1.8×10^{10} CFU; SD, standard deviation; CI, confidence interval

^a From an ANCOVA model correcting for baseline weight and sex.

^b Adjusted p-values were calculated using Benjamini-Hochberg correction.

Supplementary Table 2. GI tolerance outcomes by visit, FAS

Visit	Category	CG (n=75)	Lo-EG (n=73)	Hi-EG ((n=70)	Lo-EG v CG p-value ^d	Hi-EG v CG p-value ^d	Hi-EG v Lo-EG p-value ^d
Stool frequency^{ab}, LS mean (95% CI)							
Visit 2		1.9 (1.6, 2.2)	1.9 (1.6, 2.2)	1.9 (1.6, 2.2)	0.943	0.943	0.943
Visit 3		1.7 (1.5, 2.0)	1.6 (1.3, 1.9)	1.5 (1.2, 1.8)	0.576	0.576	0.576
Stool consistency score^{ab}, LS mean (95% CI)							
Visit 2		2.9 (2.8, 3.0)	2.9 (2.8, 3.0)	2.8 (2.7, 2.9)	0.742	0.155	0.161
Visit 3		2.8 (2.7, 3.0)	2.8 (2.7, 2.9)	2.8 (2.6, 2.9)	0.754	0.754	0.754
Stool consistency^a, N stools (%)							
Visit 2	Watery	3 (0.7%)	4 (1.0%)	19 (4.9%)	0.021	<0.0001	<0.0001
	Runny	82 (18.9%)	76 (18.4%)	103 (26.4%)			
	Soft	299 (68.7%)	309 (75.0%)	241 (61.8%)			
	Formed	48 (11.0%)	21 (5.1%)	27 (6.9%)			
	Hard	3 (0.7%)	2 (0.5%)	0 (0%)			
Visit 3	Watery	12 (3.1%)	8 (2.3%)	14 (4.5%)	0.490	0.308	0.490
	Runny	73 (18.7%)	79 (22.6%)	74 (23.8%)			
	Soft	268 (68.7%)	235 (67.3%)	204 (65.6%)			
	Formed	33 (8.5%)	26 (7.4%)	19 (6.1%)			
	Hard	4 (1.0%)	1 (0.3%)	0 (0%)			
Difficulty passing stool^{ac}, N stools (%)							
Visit 2		6 (2.7%)	4 (1.8%)	2 (1.0%)	0.513	0.495	0.513
Visit 3		2 (0.9%)	1 (0.5%)	1 (0.5%)	0.915	0.915	0.956
Regurgitation/Vomiting, N reports (%)							
Visit 2	0 times	97 (43.1%)	99 (45.2%)	117 (55.7%)	0.125	0.031	0.052
	1 time	31 (13.8%)	42 (19.2%)	32 (15.2%)			
	2-3 times	72 (32.0%)	67 (30.6%)	46 (21.9%)			
	4-6 times	20 (8.9%)	9 (4.1%)	15 (7.1%)			
	7 or more	5 (2.2%)	2 (0.9%)	0 (0%)			

Visit	Category	CG (n=75)	Lo-EG (n=73)	Hi-EG (n=70)	Lo-EG v CG p-value ^d	Hi-EG v CG p-value ^d	Hi-EG v Lo-EG p-value ^d
Regurgitation/Vomiting con't, N reports (%)							
Visit 3	0 times	142 (63.1%)	146 (66.7%)	136 (64.8%)	0.006	0.044	0.006
	1 time	26 (11.6%)	17 (7.8%)	36 (17.1%)			
	2-3 times	43 (19.1%)	55 (25.1%)	35 (16.7%)			
	4-6 times	12 (5.3%)	1 (0.5%)	3 (1.4%)			
	7 or more	2 (0.9%)	0 (0%)	0 (0%)			
Flatulence, N reports (%)							
Visit 2	0 times	171 (76.0%)	182 (83.1%)	156 (74.3%)	0.087	0.928	0.087
	1 time	15 (6.7%)	15 (6.8%)	18 (8.6%)			
	2-3 times	32 (14.2%)	15 (6.8%)	31 (14.8%)			
	4-6 times	5 (2.2%)	7 (3.2%)	4 (1.9%)			
	7 or more	2 (0.9%)	0 (0%)	1 (0.5%)			
Visit 3	0 times	200 (88.9%)	200 (91.3%)	180 (85.7%)	0.141	0.141	0.243
	1 time	7 (3.1%)	11 (5.0%)	17 (8.1%)			
	2-3 times	18 (8.0%)	8 (3.7%)	12 (5.7%)			
	4-6 times	0 (0%)	0 (0%)	1 (0.5%)			
	7 or more	0 (0%)	0 (0%)	0 (0%)			
Crying/fussiness, N reports (%)							
Visit 2	0 times	224 (99.6%)	212 (96.8%)	205 (97.6%)	0.066	0.133	0.876
	1 time	1 (0.4%)	1 (0.5%)	1 (0.5%)			
	2-3 times	0 (0%)	6 (2.7%)	4 (1.9%)			
Visit 3	0 times	225 (100.0%)	217 (99.1%)	210 (100.0%)	0.485	n/a	0.499
	1 time	0 (0%)	0 (0%)	0 (0%)			
	2-3 times	0 (0%)	2 (0.9%)	0 (0%)			

CG, control group (placebo supplement); Lo-EG, low-dose *B. infantis*, 1.0×10^8 CFU; Hi-EG, high-dose *B. infantis*, 1.8×10^{10} CFU; LS mean, least squares mean; CI, confidence interval. Includes all measurements in the 1 day prior to Visit 1 and in the 3-day period prior to Visits 2 and 3.

^aData were analyzed by ANCOVA and adjusted for baseline values.

^bAverage scores over the 1 day prior to baseline, or the three days prior to V2 and V3 were analyzed.

^cCalculated as the percentage of days with difficulties passing stool divided by total number of days on study.

^dAdjusted p-values were calculated using Benjamini-Hochberg correction.

Supplementary Table 3. Physician-reported adverse events, FAS

	CG (n=75)		Lo-EG (n=73)		Hi-EG (n=70)	
	No. Events	N (%)	No. Events	N (%)	No. Events	N (%)
All adverse events	38	32 (42.7%)	33	27 (37.0%)	34	27 (38.6%)
Serious adverse events	1	1 (1.3%)	0	0 (0%)	0	0 (0%)
Severity of Adverse Events						
Mild	35	31 (41.3%)	32	27 (37.0%)	33	27 (38.6%)
Moderate	1	1 (1.3%)	1	1 (1.4%)	1	1 (1.4%)
Severe	2	1 (1.3%)	0	0 (0%)	0	0 (0%)
Adverse events of interest, N (%)						
Upper respiratory infection		9 (12.0%)		3 (4.1%)		6 (8.6%)
Lower respiratory infection		6 (8.0%)		5 (6.8%)		7 (10.0%)
Otitis/ear infection		0 (0%)		0 (0%)		0 (0%)
Skin allergy		1 (1.3%)		0 (0%)		0 (0%)
GI-related/diarrhea		0 (0%)		1 (1.4%)		0 (0%)

CG, control group (placebo supplement); Lo-EG, low-dose *B. infantis*, 1.0×10^8 CFU; Hi-EG, high-dose *B. infantis*, 1.8×10^{10} CFU

Supplementary Table 4. Parent reported symptoms, FAS

Symptom	CG (n=75) N (%)	Lo-EG (n=73) N (%)	Hi-EG1 (n=70) N (%)	Lo-EG vs CG p-value	Hi-EG vs CG p-value	Hi-EG vs Lo- EG p-value
Fever^a	16 (21.3%)	23 (31.5%)	18 (25.7%)		0.369	
Duration ^b						
1 day	9 (12.0%)	13 (17.8%)	7 (10.0%)			
2 days	2 (2.7%)	6 (8.2%)	4 (5.7%)	0.746	0.746	>0.99
3 days	1 (1.3%)	0 (0.0%)	0 (0.0%)			
Fever^a, excluding vaccine-induced fever¹	5 (6.7%)	7 (9.6%)	8 (11.4%)		0.604	
Duration ^b						
1 day	1 (1.3%)	3 (4.1%)	1 (1.4%)			
2 days	0 (0%)	1 (1.4%)	2 (2.9%)	>0.99	>0.99	>0.99
Respiratory tract symptoms^{a,c}	17 (22.7%)	7 (9.6%)	10 (14.3%)		0.085	
Duration ^b						
2 days	2 (2.7%)	1 (1.4%)	0 (0%)			
3 days	5 (6.7%)	3 (4.1%)	5 (7.1%)	>0.99	0.705	0.705
Gastrointestinal symptoms^a	0 (0%)	1 (1.4%)	1 (1.4%)		0.976	
Duration ^b						
3 days	0 (0%)	1 (1.4%)	1 (1.4%)	n/a	n/a	n/a

CG, control group (placebo supplement); Lo-EG, low-dose *B. infantis*, 1.0×10^8 CFU; Hi-EG, high-dose *B. infantis*, 1.8×10^{10} CFU.

^a p-value from chi-square test comparing proportions between groups

^b p-value from Fisher-Halton test comparing duration between pairwise groups. Adjusted using Benjamini-Hochberg correction. Symptom duration was available for the subset of symptoms confirmed by a PI.

^c Predefined symptoms include cough, nasal congestion, sneezing, cackles/rales/wheezing, fever, difficulty breathing, hoarseness, rapid breathing, noisy breathing, and shallow breathing.

Supplementary Table 5a. Fecal pH (wet feces) and organic acids (dry feces, umol/g) at visits 2 and 3, FAS population (all subjects)

Marker	Visit	Lo-EG v CG		Hi-EG v CG		Hi-EG vs Lo-EG				
		CG (n=75)	Lo-EG (n=73)	Hi-EG (n=70)	Unadj p-value	Adj p-value	Unadj p-value	Adj p-value		
Fecal pH	Visit 2	5.38 (5.19, 5.57)	5.42 (5.22, 5.61)	5.10 (4.90, 5.30)	0.78	0.78	0.051	0.076	0.027	0.076
	Visit 3	5.31 (5.06, 5.57)	5.36 (5.10, 5.61)	5.52 (5.25, 5.78)	0.82	0.82	0.28	0.59	0.39	0.59
Acetate	Visit 2	354.6 (313.6, 395.6)	406.3 (365.3, 447.3)	456.2 (414.3, 498.1)	0.080	0.095	0.0008	0.0023	0.095	0.095
	Visit 3	437.1 (388.8, 485.5)	481.5 (433.9, 529.1)	469.7 (420.3, 519.2)	0.20	0.53	0.35	0.53	0.74	0.74
Butyrate	Visit 2	26.3 (16.4, 36.3)	38.6 (28.7, 48.6)	31.5 (21.4, 41.7)	0.086	0.26	0.47	0.47	0.32	0.47
	Visit 3	33.1 (22.7, 43.4)	42.2 (32.0, 52.4)	42.8 (32.2, 53.4)	0.22	0.32	0.20	0.32	0.94	0.94
Isobutyrate	Visit 2	5.91 (3.97, 7.85)	5.89 (3.97, 7.81)	5.85 (3.71, 8.00)	0.99	0.99	0.97	0.99	0.98	0.99
	Visit 3	7.19 (4.87, 9.52)	5.68 (3.58, 7.78)	6.96 (4.78, 9.14)	0.34	0.61	0.89	0.89	0.41	0.61
Isovalerate	Visit 2	2.10 (1.52, 2.69)	2.52 (1.94, 3.11)	1.90 (1.31, 2.50)	0.32	0.47	0.64	0.64	0.14	0.43
	Visit 3	2.53 (1.70, 3.35)	3.28 (2.46, 4.09)	2.88 (2.03, 3.72)	0.21	0.56	0.56	0.56	0.50	0.56
Propionate	Visit 2	71.4 (57.1, 85.7)	68.5 (54.2, 82.8)	65.0 (50.3, 79.6)	0.78	0.78	0.53	0.78	0.73	0.78
	Visit 3	81.0 (63.0, 99.0)	80.8 (63.1, 98.6)	87.4 (69.0, 105.8)	0.99	0.99	0.63	0.94	0.62	0.94
Valerate	Visit 2	2.61 (1.37, 3.84)	4.37 (3.13, 5.60)	3.18 (1.91, 4.44)	0.048	0.14	0.52	0.52	0.19	0.28
	Visit 3	2.61 (1.37, 3.84)	4.37 (3.13, 5.60)	5.43 (3.71, 7.16)	0.42	0.53	0.16	0.47	0.53	0.53

CG, control group (placebo supplement); Lo-EG, low-dose *B. infantis*, 1.0×10^8 CFU; Hi-EG, high-dose *B. infantis*, 1.8×10^{10} CFU. Data presented are LS mean (95% Confidence Interval) from ANCOVA model adjusted for baseline value. P-value from ANCOVA adjusted for baseline value. P-values are uncorrected.

Supplementary Table 5b. Fecal pH (wet feces) and organic acids (dry feces, umol/g) at visits 2 and 3, FAS population (breastfed only subjects)

Marker	Visit	Lo-EG v CG		Hi-EG v CG		Hi-EG vs Lo-EG				
		CG (n=42)	Lo-EG (n=42)	Hi-EG (n=41)	Unadj p-value	Adj p-value	Unadj p-value	Adj p-value		
Fecal pH	Visit 2	5.21 (4.99, 5.42)	5.03 (4.81, 5.24)	4.88 (4.67, 5.10)	0.24	0.36	0.037	0.12	0.36	0.36
	Visit 3	5.06 (4.75, 5.37)	4.96 (4.65, 5.27)	5.15 (4.84, 5.46)	0.64	0.69	0.69	0.69	0.39	0.69
Acetate	Visit 2	339.2 (283.0, 395.3)	414.1 (358.7, 469.6)	467.0 (410.1, 523.8)	0.063	0.094	0.002	0.0059	0.19	0.19
	Visit 3	394.6 (328.6, 460.5)	498.3 (434.5, 562.1)	490.8 (425.3, 556.4)	0.028	0.066	0.044	0.066	0.87	0.87
Butyrate	Visit 2	24.6 (13.6, 35.6)	23.8 (12.9, 34.7)	26.0 (14.9, 37.2)	0.92	0.92	0.85	0.92	0.78	0.92
	Visit 3	28.5 (15.2, 41.8)	32.3 (19.4, 45.3)	36.0 (22.8, 49.3)	0.68	0.69	0.43	0.69	0.69	0.69
Isobutyrate	Visit 2	4.12 (2.26, 5.97)	3.63 (1.59, 5.66)	5.70 (3.32, 8.08)	0.72	0.72	0.29	0.44	0.19	0.44
	Visit 3	3.62 (1.34, 5.90)	2.73 (0.20, 5.26)	6.35 (4.12, 8.58)	0.60	0.60	0.092	0.14	0.039	0.12
Isovalerate	Visit 2	1.55 (1.02, 2.08)	1.56 (1.04, 2.09)	1.50 (0.96, 2.04)	0.98	0.98	0.89	0.98	0.87	0.98
	Visit 3	1.83 (0.86, 2.81)	2.47 (1.51, 3.42)	2.51 (1.53, 3.49)	0.36	0.54	0.34	0.54	0.95	0.95
Propionate	Visit 2	40.6 (25.7, 55.5)	51.6 (36.9, 66.3)	33.6 (18.5, 48.7)	0.30	0.45	0.51	0.51	0.092	0.28
	Visit 3	44.8 (28.0, 61.6)	47.2 (30.9, 63.6)	66.6 (49.8, 83.4)	0.84	0.84	0.071	0.16	0.10	0.16
Valerate	Visit 2	2.48 (1.29, 3.67)	2.62 (1.44, 3.80)	2.65 (1.45, 3.86)	0.87	0.97	0.84	0.97	0.97	0.97
	Visit 3	3.32 (1.32, 5.33)	3.59 (1.64, 5.55)	5.10 (3.10, 7.10)	0.85	0.85	0.22	0.43	0.29	0.43

CG, control group (placebo supplement); Lo-EG, low-dose *B. infantis*, 1.0×10^8 CFU; Hi-EG, high-dose *B. infantis*, 1.8×10^{10} CFU. Data presented are LS mean (95% Confidence Interval) from ANCOVA model adjusted for baseline value. P-value from ANCOVA adjusted for baseline value. Adjusted p-values were calculated using Benjamini-Hochberg correction.

Supplementary Table 6. Fecal biomarkers (dry feces) at visits 2 and 3, FAS population

Marker	Visit	CG	Lo-EG	Hi-EG	Lo-EG v CG		Hi-EG v CG		Hi-EG vs Lo-EG	
					Unadj p-value	Adj p-value	Unadj p-value	Adj p-value	Unadj p-value	Adj p-value
All Subjects										
Alpha-1-Antitrypsin (mg/g)	Visit 2	2.20 (1.68, 2.72)	2.81 (2.29, 3.33)	3.14 (2.61, 3.67)	0.11	0.16	0.014	0.042	0.38	0.38
	Visit 3	4.34 (3.55, 5.13)	5.13 (4.33, 5.94)	4.16 (3.35, 4.97)	0.17	0.25	0.75	0.75	0.094	0.25
Calprotectin (mg/kg)	Visit 2	1624.5 (1260.1, 1989.0)	1433.2 (1065.8, 1800.5)	1464.3 (1079.1, 1829.5)	0.47	0.78	0.52	0.78	0.94	0.94
	Visit 3	2307.9 (1708.1, 2907.8)	2548.2 (1935.0, 3161.3)	2866.7 (2269.1, 3504.3)	0.58	0.58	0.19	0.56	0.44	0.58
sIgA (mg/kg)	Visit 2	44445.8 (34325.2, 54566.4)	50550.3 (40360.9, 60739.7)	53841.8 (43436.0, 64247.6)	0.40	0.60	0.20	0.60	0.66	0.66
	Visit 3	56355.2 (45366.4, 67344.0)	61438.7 (50220.2, 72657.2)	56756.7 (45457.9, 68055.5)	0.52	0.84	0.96	0.96	0.56	0.84
Breastfed only Subjects										
Alpha-1-Antitrypsin (mg/g)	Visit 2	2.147 (1.366, 2.928)	3.165 (2.393, 3.938)	3.378 (2.598, 4.159)	0.069	0.10	0.029	0.087	0.70	0.70
	Visit 3	4.369 (3.165, 5.572)	5.915 (4.709, 7.120)	4.279 (3.075, 5.484)	0.060	0.11	0.92	0.92	0.075	0.11
Calprotectin (mg/kg)	Visit 2	1503.3 (1100.7, 1906.0)	1322.4 (924.3, 1720.4)	1122.7 (719.6, 1525.7)	0.53	0.53	0.19	0.53	0.49	0.53
	Visit 3	2313.0 (1389.0, 3236.9)	2788.2 (1863.7, 3712.8)	2968.2 (2043.3, 3893.0)	0.47	0.71	0.32	0.71	0.79	0.79
sIgA (mg/kg)	Visit 2	53339.5 (38771.9, 67907.1)	64608.1 (50229.2, 78986.9)	60772.2 (46217.2, 75327.1)	0.28	0.71	0.48	0.71	0.71	0.71
	Visit 3	69966.2 (535972, 863353)	76733.3 (603802, 930863)	65054.7 (48700.8, 81408.5)	0.56	0.68	0.68	0.68	0.32	0.68

CG, control group (placebo supplement); Lo-EG, low-dose *B. infantis*, 1.0×10^8 CFU; Hi-EG, high-dose *B. infantis*, 1.8×10^{10} CFU. Data presented LS mean (95% Confidence Interval) from ANCOVA model adjusted for baseline value. Adjusted p-values were calculated using Benjamini-Hochberg correction.

Supplementary Table 7. Descriptive statistics for cytokines at visits 2 and 3, FAS population, all subjects

Marker	Visit	CG (n=75)	Lo-EG (n=73)	Hi-EG (n=70)
		% out of range Median [Q1, Q3]	% out of range Median [Q1, Q3]	% out of range Median [Q1, Q3]
IFN-β	Visit 2	56.0% 2.87 [1.79, 5.41]	37.0% 2.10 [1.12, 4.09]	55.7% 2.02 [1.03, 3.42]
	Visit 3	37.3% 2.06 [1.06, 3.81]	38.4% 3.07 [1.49, 3.81]	50.0% 1.98 [0.82, 5.45]
IFN-γ	Visit 2	30.7% 0.53 [0.34, 1.34]	34.2% 0.42 [0.24, 0.78]	38.6% 0.40 [0.28, 0.60]
	Visit 3	24.0% 0.62 [0.36, 1.12]	21.9% 0.57 [0.29, 1.14]	35.7% 0.55 [0.29, 0.82]
IL-10	Visit 2	98.7% 0.32 [0.32, 0.32]	90.4% 0.04 [0.04, 0.05]	97.1% 0.03 [0.03, 0.04]
	Visit 3	89.3% 0.09 [0.05, 0.10]	83.6% 0.05 [0.03, 0.09]	85.7% 0.08 [0.03, 0.14]
IL-13	Visit 2	85.3% 0.55 [0.47, 0.68]	86.3% 0.54 [0.37, 0.93]	81.4% 0.59 [0.40, 0.78]
	Visit 3	80.0% 0.83 [0.56, 1.10]	79.5% 0.54 [0.43, 0.63]	81.4% 0.83 [0.55, 0.85]
IL-17A Gen.B	Visit 2	72.0% 1.17 [0.63, 1.78]	68.5% 0.94 [0.55, 1.43]	81.4% 0.83 [0.72, 0.89]
	Visit 3	68.0% 0.85 [0.53, 1.27]	68.5% 0.78 [0.67, 1.07]	75.7% 0.75 [0.54, 1.16]
IL-1β	Visit 2	5.3% 1.834 [0.63, 4.83]	2.7% 1.39 [0.40, 3.13]	11.4% 0.97 [0.46, 2.71]
	Visit 3	8.0% 1.12 [0.33, 4.31]	12.3% 0.92 [0.39, 2.62]	10.0% 0.68 [0.21, 2.85]
IL-6	Visit 2	86.7% 0.10 [0.06, 0.13]	82.2% 0.09 [0.07, 0.11]	77.1% 0.11 [0.06, 0.16]
	Visit 3	69.3% 0.12 [0.08, 0.18]	61.6% 0.09 [0.07, 0.16]	62.9% 0.08 [0.07, 0.13]
IL-8	Visit 2	8.0% 1.68 [0.49, 3.71]	12.3% 0.85 [0.38, 1.97]	5.7% 0.81 [0.42, 3.17]
	Visit 3	14.7% 1.59 [0.57, 5.15]	4.1% 0.95 [0.42, 2.62]	5.7% 1.16 [0.49, 3.46]
IL-21	Visit 2	56.0% 3.86 [2.86, 5.44]	64.4% 2.92 [2.46, 4.10]	57.1% 3.16 [2.30, 3.50]
	Visit 3	62.7% 3.82 [2.64, 4.62]	67.1% 3.09 [2.26, 4.05]	61.4% 2.72 [2.02, 4.25]
IL-22	Visit 2	94.7% 1.20 [0.60, 2.54]	100% 0.37 [0.24, 0.50]	95.7% 0.25 [0.24, 0.77]
	Visit 3	88.0% 0.59 [0.42, 1.09]	94.5% 0.37 [0.24, 0.50]	97.1% 0.88 [0.37, 1.40]
IL-23	Visit 2	25.3% 1.91 [1.39, 2.74]	43.8% 2.13 [1.60, 3.38]	31.4% 2.06 [1.35, 3.66]

Marker	Visit	CG (n=75)	Lo-EG (n=73)	Hi-EG (n=70)
		% out of range Median [Q1, Q3]	% out of range Median [Q1, Q3]	% out of range Median [Q1, Q3]
IL-27	Visit 3	26.7% 1.87 [1.46, 2.69]	27.4% 2.34 [1.34, 3.78]	30.0% 1.68 [1.24, 2.56]
	Visit 2	38.7% 19.23 [15.10, 51.18]	32.9% 17.73 [12.48, 31.46]	30.0% 17.49 [12.11, 28.52]
	Visit 3	32.0% 18.31 [10.66, 31.42]	27.4% 14.47 [10.26, 23.77]	38.6% 12.85 [8.68, 21.88]
IL-31	Visit 2	98.7% 1.33 [1.33, 1.33]	98.6% 0.87 [0.87, 0.87]	95.7% 0.62 [0.53, 0.90]
	Visit 3	96.0% 0.48 [0.48, 0.48]	97.3% 0.48 [0.48, 0.48]	100% 0.48 [0.48, 0.48]
IL-33	Visit 2	93.3% 0.10 [0.07, 0.43]	84.9% 1.11 [0.06, 0.12]	84.3% 0.09 [0.07, 0.20]
	Visit 3	73.3% 0.22 [0.11, 0.30]	64.4% 0.17 [0.09, 0.31]	81.4% 0.22 [0.14, 0.48]
MIP-3 α	Visit 2	65.3% 1.33 [1.07, 3.02]	60.3% 1.09 [0.80, 2.50]	60.0% 1.06 [0.71, 1.50]
	Visit 3	69.3% 1.35 [0.94, 1.90]	56.2% 1.36 [1.11, 1.93]	75.7% 0.735 [0.64, 0.95]
TNF- α	Visit 2	73.3% 0.08 [0.07, 0.12]	58.9% 0.11 [0.08, 0.1.6]	67.1% 0.12 [0.11, 0.17]
	Visit 3	54.7% 0.14 [0.10, 0.19]	58.9% 0.14 [0.10, 0.20]	58.6% 0.13 [0.10, 0.15]

Units: pg/mg; CG, control group (placebo supplement); Lo-EG, low-dose *B. infantis*, 1.0×10^8 CFU; Hi-EG, high-dose *B. infantis*, 1.8×10^{10} CFU.

Supplementary Table 8. ANCOVA results for cytokines with at least 50% of values above limit of detection at visits 2 and 3, FAS population, all subjects and breastfed only subjects

Marker	Visit	Lo-EG v CG			Hi-EG v CG			Hi-EG v Lo-EG		
		LS mean difference (95% CI)	Unadjusted p-value	Adjusted p-value	LS mean difference (95% CI)	Unadjusted p-value	Adjusted p-value	LS mean difference (95% CI)	Unadjusted p-value	Adjusted p-value
All subjects										
IFN- γ	Visit 2	-0.067 (-3.48, 3.34)	0.97	0.97	1.87 (-1.59, 5.33)	0.29	0.43	1.94 (-1.58, 5.45)	0.28	0.43
	Visit 3	-0.11 (-0.90, 0.69)	0.79	0.79	-0.61 (-1.43, 0.20)	0.14	0.34	-0.51 (-1.33, 0.32)	0.23	0.34
IL-1 β	Visit 2	-2.05 (-4.48, 0.38)	0.097	0.15	-2.83 (-5.40, -0.26)	0.031	0.09	-0.78 (-3.31, 1.75)	0.54	0.54
	Visit 3	-2.29 (-5.11, 0.52)	0.11	0.33	-1.69 (-4.54, 1.16)	0.24	0.37	0.60 (-2.29, 3.49)	0.68	0.68
IL-8	Visit 2	-1.52 (-4.00, 0.96)	0.23	0.52	-0.33 (-2.72, 2.06)	0.78	0.78	1.19 (-1.30, 3.68)	0.35	0.52
	Visit 3	-1.84 (-5.42, 1.74)	0.31	0.47	-0.003 (-3.49, 3.49)	>0.99	>0.99	1.84 (-1.67, 5.34)	0.30	0.47
IL-23	Visit 2	2.90 (-3.48, 9.27)	0.37	0.55	-0.56 (-6.55, 5.44)	0.85	0.85	-3.45 (-9.63, 2.72)	0.27	0.55
	Visit 3	-3.84 (-10.96, 3.29)	0.29	0.68	-1.47 (-8.43, 5.49)	0.68	0.68	2.36 (-4.23, 8.96)	0.48	0.68
	Visit 2	-10.87 (-29.69, 7.94)	0.25	0.42	-10.39 (-29.31, 8.53)	0.28	0.42	0.48 (-18.24, 19.20)	0.96	0.96
IL-27	Visit 3	-8.71 (-30.46, 13.05)	0.43	0.55	-15.53 (-38.43, 7.36)	0.18	0.54	-6.82 (-29.50, 15.80)	0.55	0.55
Breastfed only subjects										
IFN- γ	Visit 2	-0.24 (-5.52, 5.03)	0.93	0.93	3.00 (-2.34, 8.34)	0.27	0.40	3.24 (-2.27, 8.75)	0.25	0.40
	Visit 3	-0.82 (-1.75, 0.10)	0.080	0.12	-0.87 (-1.80, 0.07)	0.070	0.12	-0.04 (-1.01, 0.92)	0.93	0.93
IL-1 β	Visit 2	-5.77 (-9.19, -2.35)	0.0011	0.0034	-4.73 (-8.28, -1.18)	0.0095	0.014	1.04 (-2.39, 4.47)	0.55	0.55
	Visit 3	-3.17 (-5.90, -0.45)	0.023	0.035	-3.97 (-6.71, -1.23)	0.0050	0.015	-0.80 (-3.50, 1.90)	0.56	0.56
IL-8	Visit 2	-3.39 (-7.10, 0.32)	0.073	0.22	-1.38 (-4.92, 2.16)	0.44	0.44	2.01 (-1.61, 5.63)	0.27	0.41
	Visit 3	-5.47 (-9.53, -1.41)	0.0087	0.026	-4.09 (-7.99, -0.18)	0.041	0.061	1.39 (-2.48, 5.26)	0.48	0.48
IL-23	Visit 2	-2.23 (-5.47, 1.01)	0.17	0.32	-2.00 (-5.18, 1.19)	0.21	0.32	0.23 (-2.80, 3.26)	0.88	0.88
	Visit 3	-0.55 (-10.85, 9.75)	0.92	0.92	3.87 (-6.62, 4.35)	0.46	0.69	4.41 (-5.06, 3.89)	0.35	0.69
	Visit 2	-8.01 (-34.05, 18.03)	0.54	0.78	-11.73 (-38.47, 15.01)	0.38	0.78	-3.72 (-30.15, 22.71)	0.78	0.78
IL-27	Visit 3	-11.64 (-43.64, 20.37)	0.47	0.71	-17.07 (-53.20, 19.06)	0.35	0.71	-5.43 (-41.46, 30.60)	0.76	0.76

CG, control group (placebo supplement); Lo-EG, low-dose *B. infantis*, 1.0×10^8 CFU; Hi-EG, high-dose *B. infantis*, 1.8×10^{10} CFU. ANCOVA includes adjustment for baseline value. Adjusted p-values were calculated using Benjamini-Hochberg correction.

Supplementary Table 9. Statistical summary of group alpha diversity differences for gene, MGS, and genus-level richness.

Visit	Taxonomical level	Diversity measure	CG Median [Q1, Q3]	Lo-EG Median [Q1, Q3]	Hi-EG Median [Q1, Q3]	Kruskal-Wallis p-value	Dunn's p-value CG Lo-EG	Dunn's p-value CG Hi-EG	Dunn's p-value Lo-EG Hi-EG
Visit 1	Gene	Richness	95871 [78841, 120174]	101899 [76456, 123403]	101519 [74321, 126164]	0.843	n/a	n/a	n/a
		Shannon	10.2 [10.0, 10.6]	10.2 [9.7, 10.5]	10.2 [9.7, 10.5]	0.687	n/a	n/a	n/a
	MGS	Richness	41 [33, 51]	42 [33, 55]	43 [30, 54]	0.981	n/a	n/a	n/a
		Shannon	1.9 [1.6, 2.2]	1.9 [1.5, 2.2]	1.9 [1.5, 2.2]	0.508	n/a	n/a	n/a
		Faith's PD	19.5 [15.3, 23.3]	19.6 [15.4, 23.1]	19.6 [15, 25]	0.894	n/a	n/a	n/a
	Genus	Richness	17 [14, 21]	17 [14, 21]	18 [14, 23]	0.754	n/a	n/a	n/a
Shannon		1.5 [1.2, 1.7]	1.3 [1, 1.7]	1.4 [0.9, 1.7]	0.401	n/a	n/a	n/a	
Visit 2	Gene	Richness	109237 [90153, 139724]	103989 [78010, 130565]	96739 [71156, 128602]	0.234	n/a	n/a	n/a
		Shannon	10.2 [9.9, 10.5]	10.1 [9.6, 10.4]	10 [9.5, 10.4]	0.074	n/a	n/a	n/a
	MGS	Richness	51 [40, 61]	47 [37, 61]	47 [33, 58]	0.434	n/a	n/a	n/a
		Shannon	1.9 [1.6, 2.2]	1.8 [1.4, 2.2]	1.7 [1.3, 2.1]	0.400	n/a	n/a	n/a
		Faith's PD	23.6 [18.9, 27.1]	22.5 [17.3, 28.7]	23.6 [17.8, 26.6]	0.984	n/a	n/a	n/a
	Genus	Richness	22 [17, 25]	20 [16, 26]	21 [14, 25]	0.524	n/a	n/a	n/a
Shannon		1.3 [1.0, 1.7]	1.1 [0.6, 1.5]	1.0 [0.7, 1.6]	0.00521	0.0045	0.00602	0.895	
Visit 3	Gene	Richness	110780 [88167, 132630]	109606 [92956, 138893]	119724 [91470, 138967]	0.510	n/a	n/a	n/a
		Shannon	10 [9.7, 10.4]	10.2 [9.8, 10.4]	10.1 [9.7, 10.5]	0.310	n/a	n/a	n/a
	MGS	Richness	51 [38, 64]	53 [41, 69]	56 [43, 70]	0.415	n/a	n/a	n/a
		Shannon	1.7 [1.4, 2.1]	1.9 [1.4, 2.2]	1.8 [1.4, 2.3]	0.468	n/a	n/a	n/a
		Faith's PD	24.7 [18.9, 29.3]	25.7 [19.5, 30.5]	24.3 [20.3, 31.1]	0.383	n/a	n/a	n/a
	Genus	Richness	24 [17, 28]	23 [17, 28]	23 [18, 29]	0.522	n/a	n/a	n/a
Shannon		1.2 [0.9, 1.6]	1.2 [0.7, 1.5]	1.1 [0.8, 1.6]	0.394	n/a	n/a	n/a	
Visit 4	Gene	Richness	129254 [107885, 163289]	128683 [102894, 157331]	123937 [87304, 156408]	0.559	n/a	n/a	n/a
		Shannon	10.3 [10, 10.6]	10.2 [9.9, 10.6]	10.1 [9.8, 10.6]	0.419	n/a	n/a	n/a
	MGS	Richness	57 [45, 78]	60 [45, 73]	56 [42, 71]	0.577	n/a	n/a	n/a
		Shannon	2.0 [1.6, 2.3]	1.9 [1.6, 2.4]	1.9 [1.4, 2.3]	0.832	n/a	n/a	n/a
		Faith's PD	27.2 [21.1, 33.6]	28.6 [21.7, 33.1]	25.2 [20.4, 31.1]	0.270	n/a	n/a	n/a
	Genus	Richness	25 [19, 32]	28 [20, 32]	23 [19, 30]	0.312	n/a	n/a	n/a
Shannon		1.4 [1.1, 1.7]	1.3 [0.9, 1.7]	1.3 [0.9, 1.7]	0.470	n/a	n/a	n/a	

CG, control group (placebo supplement); Lo-EG, low-dose *B. infantis*, 1.0×10^8 CFU; Hi-EG, high-dose *B. infantis*, 1.8×10^{10} CFU. Shannon diversity (Shannon), and MGS-level Faith's Phylogenetic distance (Faith's PD). Pairwise comparisons using Dunn's test were applied for measures significantly different in the Kruskal-Wallis test.

Supplementary Table 10. PERMANOVA R² and p-values based on 1,000 permutations for overall and pairwise comparisons of Bray-Curtis dissimilarity and weighted UniFrac distance between groups at each visit.

Visit	Comparisons	Bray-Curtis		Weighted UniFrac	
		R ²	p-value	R ²	p-value
Visit 1	All	0.87%	0.560	0.92%	0.398
	CG vs Lo-EG	0.58%	0.654	1.22%	0.093
	CG vs Hi-EG	0.73%	0.405	0.78%	0.297
	Lo-EG vs Hi-EG	0.66%	0.536	0.05%	0.988
Visit 2	All	4.93%	0.001	3.1%	0.012
	CG vs Lo-EG	5.13%	0.001	2.94%	0.007
	CG vs Hi-EG	5.00%	0.001	3.52%	0.012
	Lo-EG vs Hi-EG	0.48%	0.713	0.18%	0.906
Visit 3	All	2.83%	0.001	1.22%	0.216
	CG vs Lo-EG	2.71%	0.001	1.26%	0.104
	CG vs Hi-EG	2.72%	0.002	1.18%	0.144
	Lo-EG vs Hi-EG	0.76%	0.341	0.19%	0.871
Visit 4	All	1.92%	0.005	0.87%	0.427
	CG vs Lo-EG	1.81%	0.003	0.82%	0.273
	CG vs Hi-EG	1.95%	0.006	0.82%	0.269
	Lo-EG vs Hi-EG	0.46%	0.768	0.29%	0.833

CG, control group (placebo supplement); Lo-EG, low-dose *B. infantis*, 1.0×10^8 CFU; Hi-EG, high-dose *B. infantis*, 1.8×10^{10} CFU.

Supplementary Table 11. Significantly different taxa between groups per visit. P-values were adjusted using FDR applied to each taxonomical rank separately. No taxa were significantly different at Visit 1.

Visit	Rank	Taxon	Median abundance (%) [IQR1; IQR3]			Kruskal-Wallis adjusted p-value	Dunn's test adjusted p-value		
			CG	Lo-EG	Hi-EG		CG v Lo-EG	CG v Hi-EG	Lo-EG v Hi-EG
Visit 2	MGS	<i>B. infantis</i>	0 [0; 0.005]	22.7 [4.3; 47.8]	21.6 [3.8; 51.5]	3.4*10 ⁻¹²	1.1*10 ⁻¹¹	1.1*10 ⁻¹¹	0.973
	genus	<i>Bifidobacterium</i>	41.5 [12.5; 70.0]	69.3 [30.7; 83.8]	66.4 [34.8; 82.7]	0.086	0.0061	0.0040	0.709
	genus	<i>Klebsiella</i>	3.85 [0.95; 15.4]	0.77 [0.14; 6.2]	1.05 [0.098; 10.4]	0.086	0.0029	0.019	0.451
	genus	<i>Mediterraneibacter</i>	0.0066 [0; 0.60]	0 [0; 0.18]	0.0023 [0; 0.017]	0.086	0.243	0.0027	0.046
	-	Infant-type Bifidobacteria	31.0 [1.3; 67.4]	59.0 [23.9; 83.0]	59.9 [26.1; 82.3]	0.00038	0.0008 0	0.0002 7	0.616
Visit 3	MGS	<i>B. infantis</i>	0 [0; 9.8]	21.8 [1.0; 53.7]	11.7 [1.7; 45.8]	3.1*10 ⁻⁷	1.7*10 ⁻⁸	2.9*10 ⁻⁷	0.574
	-	Infant-type Bifidobacteria	41.9 [8.8; 67.9]	61.8 [19.6; 81.0]	61.4 [25.0; 79.7]	0.038	0.013	0.013	0.949
Visit 4	MGS	<i>B. infantis</i>	0 [0; 1.5]	14.6 [0.02; 44.1]	11.9 [0.05; 51.4]	0.00020	8.8*10 ⁻⁶	8.8*10 ⁻⁶	0.982
	MGS	<i>Lachnospiraceae sp.</i>	0.0 [0.0; 0.0]	0.0 [0.0; 0.0]	0.0 [0.0; 0.0]	0.0082	0.0008 2	0.0001 4	0.512
	-	Infant-type Bifidobacteria	48.2 [12.9; 63.6]	52.2 [22.8; 76.5]	60.8 [28.8; 80.7]	0.0832	0.038	0.034	0.743

CG, control group (placebo supplement); Lo-EG, low-dose *B. infantis*, 1.0 x 10⁸ CFU; Hi-EG, high-dose *B. infantis*, 1.8 x 10¹⁰ CFU. IQR, Inter Quartile Range. P-values were adjusted using FDR applied to each taxonomical rank separately. No taxa were significantly different at Visit 1.

Supplementary Table 12. Prevalence of pathogenic species identified by detection of specific virulence factors among groups and visits.

Pathogen	Visit	CG	Lo-EG	Hi-EG
<i>Campylobacter</i> spp.	V1	0	1 (1.4%)	0
	V2	0	1 (1.4%)	2 (2.9%)
	V3	4 (5.5%)	0	0
	V4	0	1 (1.4%)	0
<i>Clostridioides difficile</i>	V1	2 (2.7%)	0	1 (1.4%)
	V2	10 (13%)	4 (5.5%)	4 (5.8%)
	V3	14 (19%)	7 (9.6%)	7 (10%)
	V4	17 (23%)	14 (19%)	10 (14%)
<i>Clostridium perfringens</i>	V1	1 (1.4%)	0	0
	V2	0	1 (1.4%)	0
	V3	0	0	0
	V4	0	0	0
<i>Escherichia coli</i>	V1	1 (1.4%)	0	0
	V2	1 (1.3%)	1 (1.4%)	0
	V3	0	0	3 (4.3%)
	V4	4 (5.3%)	2 (2.7%)	3 (4.3%)

CG, control group (placebo supplement); Lo-EG, low-dose *B. infantis*, 1.0×10^8 CFU; Hi-EG, high-dose *B. infantis*, 1.8×10^{10} CFU. Numbers in brackets refer to the percentage of all infants in the group at the visit.

Supplementary Table 13. Chi-squared test p-values for overall and pairwise differences in FCT profiles between samples stratified according to *B. infantis* strain colonization at V4.

Visit	p-value (overall)	p-value (pairwise; LMG11588 vs No B. infantis)	p-value (pairwise; Other B. infantis vs No B. infantis)	p-value (pairwise; Other B. infantis vs LMG11588)
Visit 1	0.009	0.020	9.47×10^{-4}	0.246
Visit 2	2.23×10^{-4}	0.001	7.11×10^{-5}	0.381
Visit 3	2.61×10^{-4}	8.48×10^{-4}	2.27×10^{-4}	0.334
Visit 4	6.12×10^{-7}	5.6×10^{-5}	2.34×10^{-5}	0.101