Text, Supplemental Digital Content 1

Human-reared infant procedures. HR infants were fed Similac Sensitive® with OptiGro, which contains prebiotics. Formula was prepared fresh by animal care staff and was mixed according to the manufacturer's instructions. Following a soak in warm water with disinfectant, used bottles and nipples were cleaned using under hot water with a bottlebrush and were sanitized daily. HR infants started with bottle-feeding 60mL of formula 6 times daily for 2 weeks, progressing to ad libitum self-feeding from a mounted bottle. HR infants were introduced to chow soaked in formula and small pieces of fruit at 2 weeks of age. At one month, HR infants were paired with another HR infant and transferred to a stainless-steel cage. At day 30, infants were now given a bottle 5 times daily and were progressively weaned from formula by 2 months.

Text, Supplemental Digital Content 2

Specimen Collection, Isolation of Bacterial DNA, and Sequence Analysis. Rectal swabs were obtained between 0930-1130 at 2, 4 or 8 weeks of age. A small quantity of fecal matter was sampled using the BBL™ CultureSwab™ Collection & Transport System swab/tube (Becton Dickinson) and stored at <-60 ºC. Extraction of genomic DNA was performed using the PowerSoil DNA Isolation Kit (MoBio, Carlsbad, CA). Purified genomic extracts were quantified using a Qubit 2.0 Fluorometer (Life Technologies, Carlsbad, CA), and stored at -20 ºC in 10 mM Tris buffer until sequenced. PCR amplification of the V4 variable region of the 16S rRNA gene using variable region-specific primers (515F-806R) and amplicon sequencing were performed on an Illumina MiSeq by the Argonne National Laboratory (Lamont, IL). Each sample generated an average 30,597 sequences. Sequences were de-multiplexed and quality filtered through QIIME default settings, and closed reference operational taxonomic unit (OTU) picking was conducted using the GreenGenes 13_8 reference database (19) to classify and group unique sequences into OTUs based on 97% nucleotide sequence identity. OTUs with fewer than 15 reads, and two samples with fewer than 1,000 filtered sequences, were excluded from further analysis.

Text, Supplemental Digital Content 3

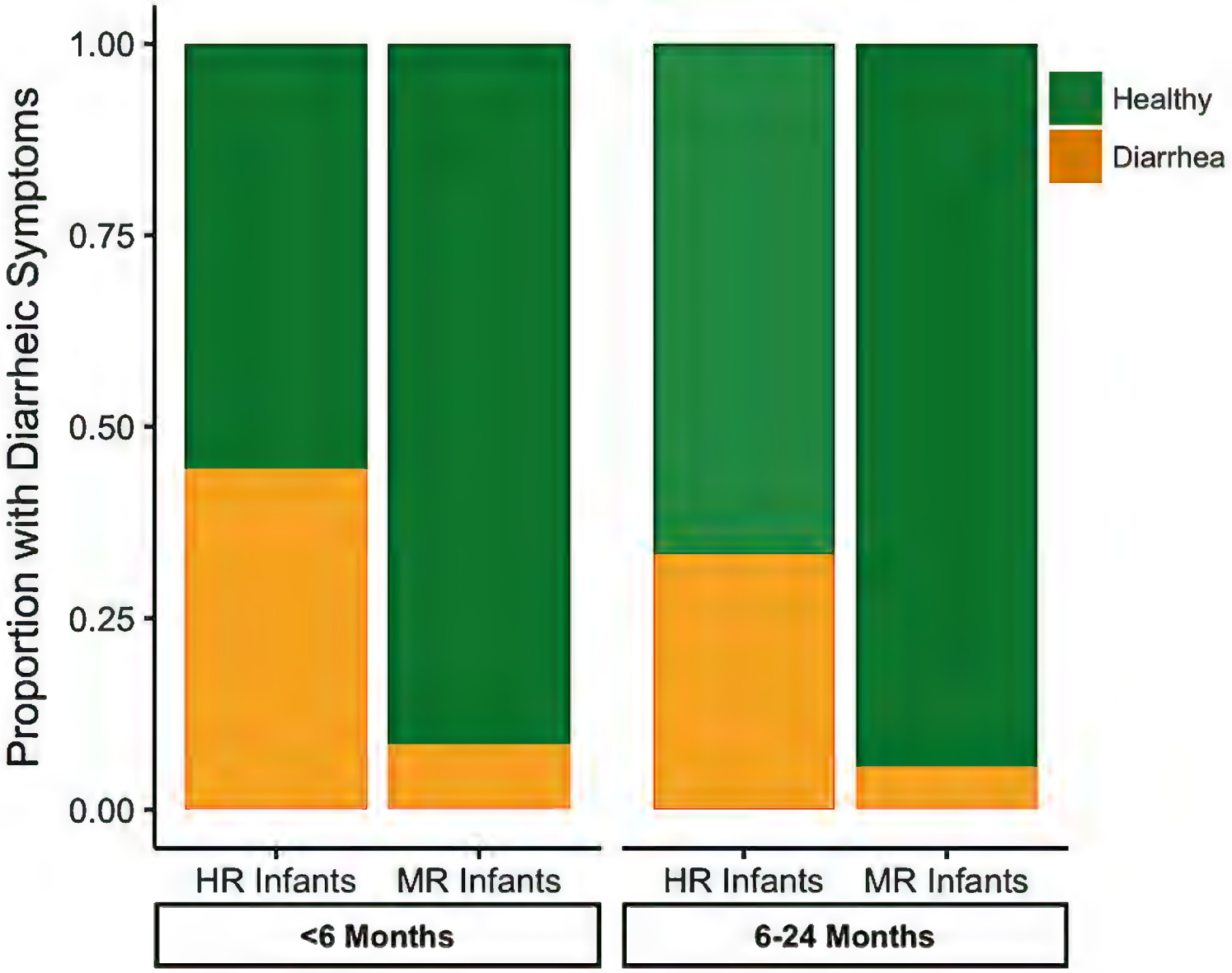
Analysis 2: Serial evaluation of MR infants. Seventeen MR infants were sampled at all 3 age points permitting a serial analysis of developmental change within each infant. Linear mixed effect modeling revealed that community richness was characterized by an increase in diversity that stabilized at 8 weeks ($F(2,16)=3.175$, $p=0.055$). However, there was no difference in beta diversity over time. Despite the relative stability of these diversity indices, the relative abundance of genera did change. *Prevotella*, the most common genera, increased to 22.8% ($F(2,32)=3.29$; $p=0.05$), with higher levels at 8 weeks than at 2 and 4 weeks ($p=0.053$; $p=0.011$, respectively). *Bifidobacteria* were second most abundant, comprising an average 15.5% of identified taxa, and the levels were stable during active nursing. *Lactobacillus* abundance diverged, increasing to 6.7% by 4 weeks of age, but decreased by nearly half as other taxa became prominent at 8 weeks ($F(2,32)=5.82$, $p=0.007$). KEGG orthologs analyses did not identify any age-related predictions in microbial gene function that survived correction for FDR in this smaller subset of MR infants.

Table, Supplemental Digital Content 4. Infant Recruitment Descriptives

	Total		Female Infants		Male Infants	
Age	MR	HR	MR	HR	MR	HR
2 weeks	34	16	20	8	14	8
4 weeks	21	5	12	2	9	3
8 weeks	19	7	12	3	7	4

Table, Supplemental Digital Content 5. Alpha Diversity Metrics

	2 Weeks			4 Weeks			8 Weeks		
Alpha Diversity Metrics	*p*	MR Mean	HR Mean	*p*	MR Mean	HR Mean	*p*	MR Mean	HR Mean
Faith's Phylogenetic Diversity	0.83	31.50	32.27	0.58	30.63	27.60	0.85	28.52	29.12
Chao1 Index	0.57	489.11	531.41	0.72	457.97	494.25	0.17	437.79	528.32
Observed OTUs	0.56	420.12	453.19	0.72	403.71	431.80	0.26	390.84	448.86



Figure, Supplemental Digital Content 6 Prevalence of diarrheic symptoms. HR infants were more likely to be treated for both acute and chronic diarrhea by 6 months of age and the increased susceptibility to enteric pathogens continued during the 6-month period following weaning. Clinical stool cultures were run on 73% of infants exhibiting symptoms; *Campylobacter jejeuni* was most common pathogen identified.