

SUPPLEMENTAL DATA

Appendix Table 1. Effect of calorie restriction on white blood cells*			
Variable (time)	Treatment Group		p-value ‡
	CR	AL	
Total monocytes (10 ³ /μL)			
Baseline	0.33 (0.01)	0.32 (0.01)	
Mo. 12	0.32 (0.01)	0.37 (0.01) †	0.004
Mo. 24	0.32 (0.01)	0.35 (0.01) †	0.034
Total Neutrophils (10 ³ /μL)			
Baseline	3.68 (0.11)	3.60 (0.13)	
Mo. 12	3.41 (0.12) †	3.71 (0.16)	0.106
Mo. 24	3.24 (0.10) †	3.54 (0.14)	0.067
Total Eosinophils (10 ³ /μL)			
Baseline	0.14 (0.01)	0.11 (0.01)	
Mo. 12	0.14 (0.01)	0.12 (0.01)	0.095
Mo. 24	0.13 (0.01)	0.15 (0.01)	0.102
Total Basophils (10 ³ /μL)			
Baseline	0.01 (0.001)	0.02 (0.002)	
Mo. 12	0.021 (0.002) †	0.025 (0.002) †	0.378
Mo. 24	0.020 (0.002) †	0.024 (0.002) †	0.443

* Results are mean (SE) and reflect predicted values at months 12 and 24 based on intention-to-treat (ITT) statistical analysis, p-values reflect the ITT analyses for changes from baseline at each time point.

† Significantly different from baseline within the same treatment group.

‡ Values reflect difference in change from baseline between treatment groups at each time point.

Appendix Table 2. Effect of calorie restriction on antibody response to Hepatitis A, Tetanus/Diphtheria and Pneumococcal vaccines						
Time (Mos.)	Median (IQR)*			% with detectable values		
	17	18	24	17	18	24
Hepatitis A (IU/L)						
AL	9.7 (7.8, 11.7)	41.7 (29.5, 53.7)	NA	42.9%	27.5%	0%†
CR	8.6 (7.5, 10.3)	37.3 (26.0, 53.0)	28.5 (16.4, 40.7)	28.0%	23.2%	5.1%†
p-value	0.601‡	0.983‡	NA	0.670	0.832	0.332
Tetanus (IU/mL)						
AL	2.43 (1.8, 3.5)	4.95 (3.8, 5.9)	3.31 (2.6, 4.1)	90.2%	51.7%	79.3%
CR	2.56 (1.7, 3.9)	4.37 (3.3, 5.7)	3.70 (2.6, 5.0)	93.1%	52.9%	79.4%
p-value	0.675	0.775	0.940	0.499‡	0.876‡	0.992‡
Diphtheria (IU/mL)						
AL	0.36 (0.2, 0.7)	1.1 (0.7, 1.9)	0.77 (0.4, 1.1)	100%	93.3%	98.3%
CR	0.35 (0.2, 0.7)	1.1 (0.7, 1.5)	0.75 (0.4, 1.3)	98%	87.3%	100%
p-value	0.350	0.644	0.901	0.273	0.416	0.196
Pneumonia IgG Serotype 1 (µg/mL)						
AL	1.5 (0.8, 4.5)	10.0 (3.7, 35.4)	8.1 (3.1, 30.5)	85.7%	95.1%	100%
CR	1.7 (0.8, 3.9)	7.0 (2.5, 23.7)	6.3 (2.9, 21.3)	77.9%	96.1%	94.6%
p-value	0.604	0.474	0.233	0.356	0.624	0.314
Pneumonia IgG Serotype 2 (µg/mL)						
AL	0.65 (0.4, 1.3)	5.5 (2.2, 9.3)	4.3 (2.1, 12.5)	88.9%	94.3%	100%
CR	0.70 (0.4, 1.5)	3.7 (1.7, 10.7)	3.5 (1.4, 9.9)	80.4%	100%	98.8%
p-value	0.437	0.553	0.296	0.185	0.448	0.456
Pneumonia IgG Serotype 3 (µg/mL)						
AL	1.0 (0.5, 2.8)	3.8 (1.6, 8.0)	2.9 (1.1, 7.7)	90.5%	98.4%	98.1%
CR	1.2 (0.5, 2.8)	3.2 (1.8, 7.1)	2.5 (1.2, 6.6)	88.3%	99.0%	98.9%
p-value	0.853	0.973	0.599	0.971	0.702	0.676
Pneumonia IgG Serotype 4 (µg/mL)						
AL	0.5 (0.2, 1.6)	1.3 (0.5, 3.6)	1.1 (0.4, 3.9)	76.2%	100%	100%
CR	0.4 (0.2, 1.0)	1.7 (0.9, 4.2)	1.2 (0.7, 3.2)	78.8%	98.1%	97.8%
p-value	0.856	0.158	0.598	0.498	1.00	1.00
Pneumonia IgG Serotype 5 (µg/mL)						
AL	2.8 (1.0, 5.2)	4.7 (2.6, 13.4)	4.1 (2.3, 11.3)	96.8%	100%	100%
CR	3.0 (1.2, 5.1)	4.5 (2.0, 12.8)	4.9 (2.1, 11.5)	95.2%	100%	100%
p-value	0.788	0.792	0.944	0.611	0.611	0.611
Pneumonia IgG Serotype 8 (µg/mL)						
AL	1.1 (0.6, 2.6)	3.5 (1.8, 7.5)	3.0 (1.5, 6.9)	100%	100%	100%
CR	1.1 (0.5, 2.6)	2.6 (1.2, 6.4)	2.6 (1.3, 5.3)	99.0%	99.0%	98.9%
p-value	0.511	0.433	0.357	0.436	0.444	0.455
Pneumonia IgG Serotype 14 (µg/mL)						
AL	3.2 (1.3, 5.2)	11.7 (4.3, 30.6)	13.6 (4.2, 29.4)	74.6%	93.4%	86.5%
CR	2.2 (1.2, 4.8)	9.7 (2.8, 31.7)	9.5 (3.0, 27.8)	72.1%	90.4%	90.3%
p-value	0.423	0.357	0.908	0.726	0.498	0.487
Pneumonia IgG Serotype 20 (µg/mL)						
AL	0.8 (0.4, 1.8)	3.0 (1.0, 11.9)	2.5 (0.9, 5.3)	79.4%	98.4%	96.2%
CR	0.8 (0.5, 1.8)	2.2 (0.9, 7.6)	2.1 (0.7, 5.9)	75.0%	94.2%	93.5%
p-value	0.777	0.215	0.514	0.723	0.503	0.910
Pneumonia IgG Serotype 6B (µg/mL)						
AL	2.5 (1.2, 5.2)	5.1 (2.8, 11.9)	4.3 (2.3, 10.2)	85.7%	93.4%	92.3%
CR	2.7 (1.4, 4.8)	5.2 (3.0, 12.7)	5.3 (2.8, 11.9)	82.7%	96.2%	92.4%
p-value	0.876	0.401	0.564	0.854	0.187	0.630

Pneumonia IgG Serotype 7F (µg/mL)						
AL	3.0 (1.7, 6.8)	5.2 (2.6, 11.4)	4.8 (2.5, 9.6)	98.4%	96.7%	98.1%
CR	2.8 (1.5, 5.3)	4.8 (2.3, 10.1)	4.8 (2.7, 9.3)	95.2%	95.2%	97.8%
p-value	0.395	0.639	0.910	0.280	0.385	0.927
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	Median (IQR)*			% with detectable values		
Time (Mos.)	17	18	24	17	18	24
Pneumonia IgG Serotype 9N (µg/mL)						
AL	1.3 (0.7, 3.2)	2.4 (1.2, 8.0)	2.5 (1.2, 6.5)	90.5%	100%	100%
CR	1.4 (0.6, 3.5)	2.8 (1.2, 6.0)	2.7 (1.2, 6.3)	77.9%	95.1%	95.7%
p-value	0.140	0.633	0.674	0.083	0.734	0.457
Pneumonia IgG Serotype 9V (µg/mL)						
AL	2.1 (1.0, 4.0)	3.9 (1.3, 11.2)	4.3 (1.7, 9.1)	95.2%	96.7%	96.2%
CR	1.9 (1.0, 4.7)	3.4 (1.6, 8.2)	3.5 (1.6, 8.4)	92.3%	96.2%	96.8%
p-value	0.636	0.162	0.215	0.461	0.851	0.845
Pneumonia IgG Serotype 10A (µg/mL)						
AL	1.9 (0.9, 5.0)	3.4 (1.6, 13.9)	2.8 (1.3, 8.0)	85.7%	88.5%	92.3%
CR	2.7 (0.9, 5.0)	3.8 (1.3, 9.5)	3.0 (1.1, 8.0)	76.9%	89.4%	89.2%
p-value	0.393	0.681	0.325	0.168	0.859	0.551
Pneumonia IgG Serotype 11A (µg/mL)						
AL	1.1 (0.5, 2.2)	3.4 (1.9, 8.8)	2.9 (1.5, 6.8)	87.3%	98.4%	100%
CR	1.2 (0.5, 4.2)	4.1 (2.0, 8.6)	3.6 (1.6, 8.1)	94.2%	100%	98.9%
p-value	0.093	0.799	0.905	0.118	0.194	0.455
Pneumonia IgG Serotype 12F (µg/mL)						
AL	0.4 (0.2, 1.0)	0.6 (0.3, 2.0)	0.7 (0.3, 2.5)	81.0%	91.8%	90.4%
CR	0.6 (0.3, 2.1)	1.2 (0.4, 3.9)	1.0 (0.4, 4.1)	74.0%	92.3%	89.2%
p-value	0.626	0.211	0.395	0.308	0.908	0.830
Pneumonia IgG Serotype 15B (µg/mL)						
AL	0.8 (0.4, 1.6)	3.7 (1.7, 13.7)	3.0 (1.5, 11.9)	84.1%	98.4%	100%
CR	0.8 (0.4, 2.0)	4.1 (1.6, 13.0)	4.0 (1.6, 10.4)	84.6%	98.1%	96.8%
p-value	0.577	0.650	0.672	0.933	0.452	0.192
Pneumonia IgG Serotype 17F (µg/mL)						
AL	3.2 (1.5, 6.4)	12.1 (4.7, 21.9)	10.3 (4.0, 19.8)	85.7%	98.4%	100%
CR	3.0 (1.6, 6.0)	11.1 (5.0, 24.8)	10.8 (5.7, 19.4)	89.4%	98.1%	97.8%
p-value	0.739	0.785	0.897	0.476	0.896	0.289
Pneumonia IgG Serotype 18C (µg/mL)						
AL	0.6 (0.3, 1.4)	3.5 (1.0, 10.2)	3.4 (1.1, 9.4)	68.3%	98.4%	92.3%
CR	0.8 (0.5, 2.0)	4.4 (1.5, 10.8)	4.3 (1.3, 8.6)	71.2%	98.1%	97.8%
p-value	0.239	0.303	0.344	0.693	0.896	0.109
Pneumonia IgG Serotype 19A (µg/mL)						
AL	4.7 (2.6, 12.5)	8.5 (3.6, 24.8)	11.3 (4.8, 23.7)	76.2%	88.3%	86.3%
CR	4.3 (2.3, 9.4)	13.0 (5.7, 38.0)	12.9 (4.8, 39.2)	79.4%	89.0%	89.9%
p-value	0.798	0.451	0.581	0.628	0.611	0.957
Pneumonia IgG Serotype 19F (µg/mL)						
AL	2.7 (1.3, 5.1)	5.2 (2.6, 16.6)	3.9 (2.0, 13.8)	74.6%	86.9%	90.4%
CR	2.9 (1.5, 5.6)	8.4 (2.9, 18.0)	5.9 (2.5, 12.0)	84.6%	91.3%	93.5%
p-value	0.063	0.228	0.256	0.062	0.200	0.254
Pneumonia IgG Serotype 22F (µg/mL)						
AL	4.2 (2.1, 8.0)	5.2 (2.7, 10.2)	4.9 (2.5, 10.6)	96.8%	95.1%	98.1%
CR	3.3 (1.6, 8.8)	3.6 (2.0, 10.1)	4.5 (2.0, 9.0)	91.3%	96.2%	95.7%
p-value	0.165	0.413	0.379	0.031	0.503	0.453

Pneumonia IgG Serotype 23F (µg/mL)						
AL	7.8 (3.2, 16.4)	8.8 (3.3, 20.0)	8.1 (3.4, 21.0)	95.2%	93.4%	96.2%
CR	7.5 (2.8, 16.2)	9.3 (3.7, 21.0)	9.6 (3.5, 18.8)	92.3%	94.2%	93.5%
p-value	0.532	0.726	0.505	0.461	0.524	0.511
Pneumonia IgG Serotype 33F (µg/mL)						
AL	1.2 (0.6, 2.9)	4.3 (1.3, 13.0)	4.4 (1.5, 11.2)	85.7%	100%	98.1%
CR	0.9 (0.5, 2.4)	5.0 (1.8, 9.6)	4.2 (1.8, 12.5)	89.4%	96.2%	97.8%
p-value	0.363	0.636	0.980	0.285	0.444	0.441

* Based on observations within detectable range. IQR, Inter-Quartile Range
† For Hepatitis A values reflect those above the detectable range.
‡ p-values are from statistical analysis accounting for censoring.
NA: Since majority of values were beyond the detectable range quantitative analysis could not be performed.

Appendix Table 3A. Annualized Rate of Infections, Allergies and Associated Medications Over the 24-Month Follow-up

Event	AL (N=75)			CR (N=143)			p-value§
	Total No. Episodes*	Average No. Days†	Annualized Rate‡	Total No. Episodes*	Average No. Days†	Annualized Rate‡	
All Infections	156	14.5	1.032	239	9.8	0.897	0.2838
Total respiratory infections	115	11.9	0.761	169	7.2	0.635	0.2099
Upper respiratory infections	108	10.9	0.715	165	6.9	0.620	0.3684
Lower respiratory infections	7	1.0	0.046	4	0.2	0.015	0.0583
GI infections	7	0.2	0.046	18	0.4	0.068	0.3602
Skin infections	9	0.7	0.060	7	0.2	0.026	0.1161
Urinary track infections	6	0.5	0.040	11	0.4	0.041	0.9154
Ear infections	4	0.3	0.026	2	0.1	0.008	0.1420
Eye infections	0	0.0	0.000	5	0.1	0.019	0.0357
Oral dental infections	6	0.3	0.040	19	0.9	0.071	0.1445
Allergies	36	1.3	0.238	47	1.2	0.176	0.1912
OTC Medication Use	190	145.0	1.257	346	229.9	1.299	0.7120
Allergy Medication Use	82	55.5	0.543	138	50.8	0.518	0.7871
Antibiotics Medication Use	71	35.6	0.470	139	33.9	0.522	0.4516

* Total number of distinct episodes summed across participants in that treatment arm.
† The total number of days during which the event was prevalent across participants in that treatment arm, divided by the number of participants in that treatment group
‡ Total number of distinct events divided by the total amount of follow-up time in that treatment arm, standardized to 365 days in a calendar year.
§ The p-value is derived from the Poisson regression model comparing the number of distinct episodes between the two groups.

Appendix Table 3B. Distribution of the Severity of the Events, Pooled Across all Events Among Participants Who Experienced the Event at Least Once

Event	AL (N=75)				CR (N=143)			
	No. Pts >=1 event*	Mild†	Moderate	Severe	No. Pts >=1 event*	Mild†	Moderate	Severe
All Infections	53	70 (44.9%)	64 (41.0%)	22 (14.1%)	89	99 (41.4%)	111 (46.4%)	29 (12.1%)
Total respiratory infections	48	51 (44.3%)	51 (44.3%)	13 (11.3%)	79	71 (42.0%)	77 (45.6%)	21 (12.4%)
Upper respiratory infections	46	49 (45.4%)	47 (43.5%)	12 (11.1%)	79	70 (42.4%)	74 (44.8%)	21 (12.7%)
Lower respiratory infections	5	2 (28.6%)	4 (57.1%)	1 (14.3%)	4	1 (25.0%)	3 (75.0%)	0
GI infections	7	2 (28.6%)	1 (14.3%)	4 (57.1%)	14	6 (33.3%)	8 (44.4%)	4 (22.2%)
Skin infections	7	6 (66.7%)	3 (33.3%)	0	7	3 (42.9%)	3 (42.9%)	1 (14.3%)
Urinary track infections	4	2 (33.3%)	3 (50.0%)	1 (16.7%)	8	1 (9.1%)	10 (90.9%)	0
Ear infections	3	0	1 (25.0%)	3 (75.0%)	2	0	0	2 (100.0%)
Eye infections	0	0	0	0	4	3 (60.0%)	2 (40.0%)	0
Oral dental infections	4	3 (50.0%)	3 (50.0%)	0	7	10 (52.6%)	8 (42.1%)	1 (5.3%)
Allergies	16	27 (75.0%)	6 (16.7%)	3 (8.3%)	23	28 (59.6%)	13 (27.7%)	6 (12.8%)

* Number of participants who experienced the event at least once in that treatment arm.

† The frequency and percent of all such events pooled across all events across all participants who experienced that event at least once.