

## Supplementary

**Table S1.** LDA scores and *p*-values associated for species in each group across time.

Species	Time Point	Group	LDA	<i>p</i> -Value
<i>Bifidobacterium pseudolongum</i>	Month 3	Neg_Control	4.962739	0.011948
<i>Methanobrevibacter unclassified</i>	Month 3	Infected	4.886258	0.000113
<i>Butyrivibrio unclassified</i>	Month 3	Infected	4.777852	0.00039
<i>Alistipes shahii</i>	Month 3	Neg_Control	4.478157	3.15E-08
<i>Parabacteroides distasonis</i>	Month 3	Neg_Control	4.346065	0.00015
<i>Bifidobacterium angulatum</i>	Month 3	Infected	4.33015	0.002528
<i>Prevotella stercorea</i>	Month 3	Neg_Control	4.134405	0.000184
<i>Bacteroides vulgatus</i>	Month 3	Neg_Control	4.097004	0.015093
<i>Subdoligranulum unclassified</i>	Month 3	Neg_Control	4.093583	0.030568
<i>Alistipes unclassified</i>	Month 3	Neg_Control	4.076705	0.011057
<i>Bifidobacterium adolescentis</i>	Month 3	Infected	4.071279	0.000218
<i>Bifidobacterium pseudolongum</i>	Month 6	Neg_Control	5.08208	3.44E-07
<i>Methanobrevibacter unclassified</i>	Month 6	Infected	4.946584	0.025121
<i>Butyrivibrio unclassified</i>	Month 6	Infected	4.933534	0.005116
<i>Butyrivibrio unclassified</i>	Month 9	Infected	4.656766	0.046088
<i>Lactobacillus buchneri</i>	Month 9	Neg_Control	4.651226	0.016779

**Table S2.** PERMANOVA and betadisper analysis for microbial community.

PERMANOVA			Betadisper	
	R <sup>2</sup>	<i>p</i> -value		<i>p</i> -value
Exposed vs. Control	0.05509	0.001	Exposed vs. Control	0.00516
Sero-positive vs. Sero-negative	0.01083	0.05	Sero-positive vs. sero-negative	0.03714
Month 3 vs. Month 6 vs. Month 9	0.23819	0.001	Month 3 vs. Month 6	0.001
			Month 3 vs. Month 9	0.001
			Month 6 vs. Month 9	0.857
Ileocecal valve enlargement present vs. absent	0.0065	0.207	Ileocecal valve enlargement present vs. absent	0.34892

**Table S3.** Superfocus level 1.

Pathway Level 1	Time Point	Group	LDA	p-Value
Membrane Transport	Month 3	Neg_Control	3.33315 4	6.36E-06
Cofactors, Vitamins, Prosthetic Groups, Pigments	Month 3	Infected	2.82187 2	0.022913
Phages, Prophages, Transposable elements Plasmids	Month 3	Neg_Control	2.74275 4	0.000169
Clustering based subsystems	Month 3	Infected	2.69593 1	0.001186
Potassium metabolism	Month 3	Neg_Control	2.68032	7.54E-05
RNA Metabolism	Month 3	Infected	2.65086 3	0.019879
Virulence	Month 3	Neg_Control	2.64941 3	0.001114
Stress Response	Month 3	Infected	2.58610 5	0.00846
Respiration	Month 3	Infected	2.57890 4	0.025152
Miscellaneous	Month 3	Infected	2.57625	0.04115
Predictions based on plant prokaryote comparative analysis	Month 3	Infected	2.47444 8	0.015598
Phages, Prophages Transposable elements	Month 3	Neg_Control	2.41896 7	0.007609
Iron acquisition and metabolism	Month 3	Neg_Control	2.38718 6	0.022913
Sulfur Metabolism	Month 3	Infected	2.36710 2	0.046781
Virulence, Disease and Defense	Month 3	Neg_Control	2.35646 2	0.014847
Regulation and Cell signaling	Month 3	Neg_Control	2.24122 6	0.01278
Carbohydrates	Month 6	Neg_Control	4.72467 5	0.006332
Protein Metabolism	Month 6	Infected	4.65829	9.88E-05
Cofactors, Vitamins, Prosthetic Groups, Pigments	Month 6	Infected	4.33813 4	0.018525
Nucleosides and Nucleotides	Month 6	Neg_Control	4.28415 9	1.28E-05
RNA Metabolism	Month 6	Infected	4.26824 4	1.70E-05
Respiration	Month 6	Infected	4.10926 1	0.003931
Fatty Acids Lipids and Isoprenoids	Month 6	Neg_Control	3.75605 5	0.0202
Phosphorus Metabolism	Month 6	Neg_Control	3.66710 3	2.41E-07

Phages, Prophages, Transposable elements, Plasmids	Month 6	Infected	3.521126	0.001005
Motility and Chemotaxis	Month 6	Neg_Control	3.313241	3.19E-05
Iron acquisition and metabolism	Month 6	Neg_Control	3.312705	0.001713
Nitrogen Metabolism	Month 6	Neg_Control	3.312471	5.45E-08
Virulence, Disease and Defense	Month 6	Neg_Control	2.972411	0.000673
Metabolism of Aromatic Compounds	Month 6	Neg_Control	2.808811	0.015362
Metabolism of Aromatic Compounds	Month 9	Infected	2.012456	0.00512
Phosphorus Metabolism	Month 9	Neg_Control	2.30226	0.027486
Nucleosides and Nucleotides	Month 9	Neg_Control	2.405557	0.025121
Cell Wall and Capsule	Month 9	Neg_Control	2.457733	0.027486
Motility and Chemotaxis	Month 9	Neg_Control	2.67589	6.16E-05

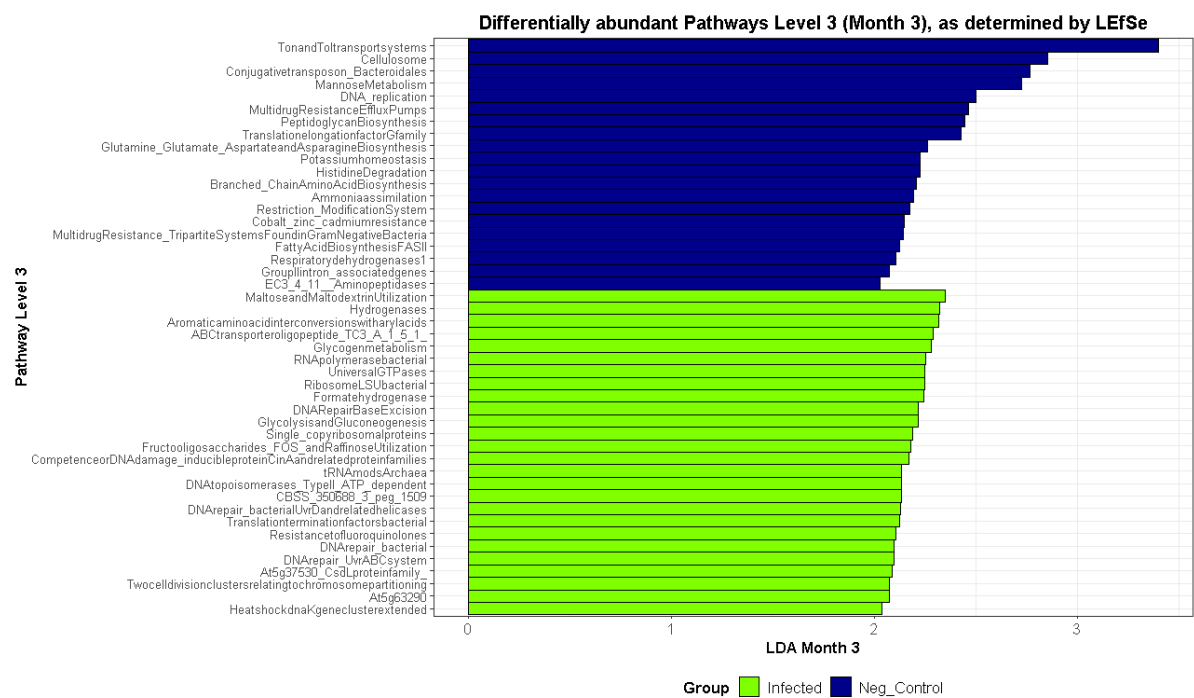
**Table S4.** Level 3 Pathways.

Pathway	Timepoint	Group	LDA	<i>p</i> Value
Ton and Tol transport systems	Month 3	Neg_Control	3.397796	6.37E-07
Cellulosome	Month 3	Neg_Control	2.852431	2.07E-06
Conjugative transposon	Month 3	Neg_Control	2.765266	1.05E-05
Bacteroidales				
Mannose Metabolism	Month 3	Neg_Control	2.725044	2.47E-06
DNA replication	Month 3	Neg_Control	2.496932	0.000711
Multidrug Resistance Efflux	Month 3	Neg_Control	2.462527	0.000109
Pumps				
Peptidoglycan Biosynthesis	Month 3	Neg_Control	2.442976	0.000258
Translation elongation factor G family	Month 3	Neg_Control	2.423262	2.81E-08

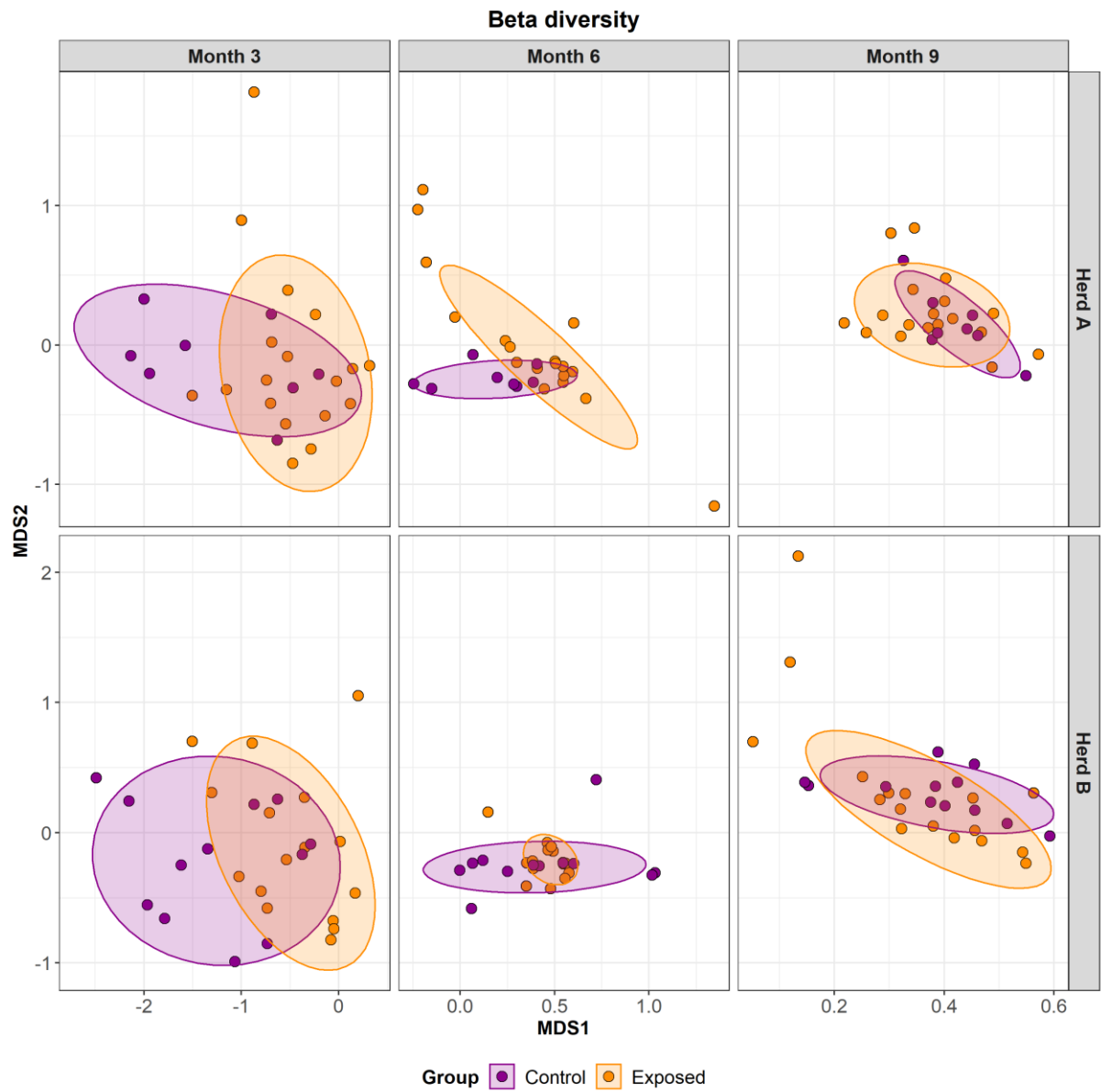
<b>Maltose and Maltodextrin Utilization</b>	Month 3	Infected	2.346961	0.027579
<b>Hydrogenases</b>	Month 3	Infected	2.319713	0.04115
<b>Aromatic amino acid interconversions with aryl acids</b>	Month 3	Infected	2.31549	0.000297
<b>ABC transporter oligopeptide</b>	Month 3	Infected	2.28926	0.018949
<b>TC3_A_1_5_1_</b>				
<b>Glycogen metabolism</b>	Month 3	Infected	2.279149	0.048796
<b>Glutamine, Glutamate, Aspartate and Asparagine Biosynthesis</b>	Month 3	Neg_Control	2.260514	0.008917
<b>RNA polymerase bacterial</b>	Month 3	Infected	2.24884	0.013439
<b>Universal GTPases</b>	Month 3	Infected	2.245888	0.00492
<b>Ribosome LSU bacterial</b>	Month 3	Infected	2.245667	0.025152
<b>Formate hydrogenase</b>	Month 3	Infected	2.241678	0.002063
<b>Potassium homeostasis</b>	Month 3	Neg_Control	2.224955	8.12E-05
<b>Histidine Degradation</b>	Month 3	Neg_Control	2.221785	0.02401
<b>DNA Repair Base Excision</b>	Month 3	Infected	2.215552	8.19E-06
<b>Glycolysis and Gluconeogenesis</b>	Month 3	Infected	2.214637	0.001263
<b>Branched Chain Amino Acid Biosynthesis</b>	Month 3	Neg_Control	2.206725	0.02401
<b>Ammonia assimilation</b>	Month 3	Neg_Control	2.189119	0.027579
<b>Single copy ribosomal proteins</b>	Month 3	Infected	2.187243	0.002191
<b>Fructooligosaccharides FOS and Raffinose Utilization</b>	Month 3	Infected	2.175969	0.014847

<b>Restriction Modification System</b>	Month 3	Neg_Control	2.173854	0.00492
<b>Competence or DNA damage</b>	Month 3	Infected	2.168221	0.000169
inducible protein CinA and related protein families				
<b>Cobalt, zinc, cadmium resistance</b>	Month 3	Neg_Control	2.147468	2.77E-05
<b>Multi drug Resistance, Tripartite</b>	Month 3	Neg_Control	2.14152	3.64E-07
Systems Found in Gram Negative Bacteria				
<b>tRNA mods Archaea</b>	Month 3	Infected	2.133358	0.003307
<b>DNA topoisomerases Type II ATP dependent</b>	Month 3	Infected	2.130945	0.000195
<b>CBSS_350688_3_peg_1509</b>	Month 3	Infected	2.129998	0.030204
<b>DNA repair bacterial UvrD and related helicases</b>	Month 3	Infected	2.126481	3.99E-07
<b>Fatty Acid Biosynthesis FASII</b>	Month 3	Neg_Control	2.12425	0.013439
<b>Translation termination factors bacterial</b>	Month 3	Infected	2.122664	0.000277
<b>Respiratory dehydrogenases 1</b>	Month 3	Neg_Control	2.105421	0.000809
<b>Resistance to fluoroquinolones</b>	Month 3	Infected	2.102699	0.001114
<b>DNA repair bacterial</b>	Month 3	Infected	2.09602	0.001618
<b>DNA repair UvrABC system</b>	Month 3	Infected	2.092834	0.001522
<b>At5g37530_CsdL protein family</b>	Month 3	Infected	2.08672	0.002777

<b>Two cell division clusters</b>	Month 3	Infected	2.070994	0.016383
relating to chromosome partitioning				
<b>GroupII intron associated genes</b>	Month 3	Neg_Control	2.070567	0.000711
<b>At5g63290</b>	Month 3	Infected	2.069919	0.005201
<b>Heatshock dnaK gene cluster</b>	Month 3	Infected	2.036021	0.006835
extended				
<b>EC3_4_11__Aminopeptidases</b>	Month 3	Neg_Control	2.02731	0.001114
<b>Na translocating NADH quinone oxidoreductase and rnf_like group of electron transport complexes</b>	Month 9	Neg_Control	2.339701	0.001069
<b>Maltose and Maltodextrin Utilization</b>	Month 9	Neg_Control	2.28345	0.001636
<b>Glycogen metabolism</b>	Month 9	Neg_Control	2.236263	0.020915
<b>Carbon monoxide induced hydrogenase</b>	Month 9	Neg_Control	2.234515	0.003289
<b>Phosphate metabolism</b>	Month 9	Neg_Control	2.227462	0.004849
<b>Flagellum</b>	Month 9	Neg_Control	2.207519	2.89E-05
<b>Multidrug Resistance Efflux Pumps</b>	Month 9	Neg_Control	2.182279	0.015757
<b>Flagellar motility</b>	Month 9	Neg_Control	2.15775	1.26E-06
<b>CBSS_393121_3_peg_2760</b>	Month 9	Neg_Control	2.145124	0.001285
<b>Inositol catabolism</b>	Month 9	Infected	2.142067	0.000437
<b>DeNovo Purine Biosynthesis</b>	Month 9	Neg_Control	2.140344	0.001137
<b>Lactose and Galactose Uptake and Utilization</b>	Month 9	Neg_Control	2.121676	0.010635
<b>Restriction Modification System</b>	Month 9	Neg_Control	2.089932	0.015757
<b>Copper homeostasis</b>	Month 9	Infected	2.086014	0.000645
<b>Omega_amidaseKE2</b>	Month 9	Neg_Control	2.073458	0.000944
<b>Translation elongation factor G family</b>	Month 9	Neg_Control	2.067573	0.000208
<b>Lacto N BioseI and Galacto_N_Biose Metabolic Pathway</b>	Month 9	Neg_Control	2.041006	0.000467
<b>Methionine Biosynthesis</b>	Month 9	Infected	2.03467	0.000103
<b>Ni Fehydrogenase maturation</b>	Month 9	Infected	2.01025	0.003108
<b>Xylose utilization</b>	Month 9	Neg_Control	2.004691	0.032797



**Figure S1.** LefSe analysis of Level 3 SUPER-FOCUS pathways in month 3.



**Figure S2.** Bray-Curtis beta diversity among animals in both the exposed and control groups, across both time and herd. Month 6 shows the microbiome becoming more stable in herd B, where samples in the exposed group are most similar. However, results were non-significant.

**Table S5.** A summary of the positive and inconclusive IDEX ELISA results during the course of the experimental challenge study, with S/P% provided. Animals which remained negative are not included. This table has been adapted from Britton, 2017.

Group	ID	Pre	M3	M6	M10	M12	M15	M16	M20	M21	M24	M27	M28	M30	M31	M33
Challenged	2155	-	-	-	-	-	-	√ 68.3	√ 95.0	√ 55.6	√ 82.6	√ 86.9	√ 109.4	-	-	-
	2176	-	-	-	-	-	-	-	√ 56.8	-	I 52.5	-	-	-	-	-
	2194	-	-	-	-	-	-	I 50.2	-	I 51.4	√ 60.7	-	I 48.7	-	I 49.2	-
	2199	-	-	-	-	-	-	-	√ 61.6	I 50.2	-					
	2201	-	-	-	-	-	-	-	I 48.4	-	-	-	-	-	-	-
	2390	-	-	-	-	-	-	-	√ 63.0	√ 63.0	-	√ 64.8	√ 67.6	I 50.4	-	-
	2402	-	-	-	-	-	-	√ 93.9	√ 84.9	√ 68.7	-	√ 84.8	√ 99.0	√ 70.8	-	-
	2413	-	-	-	-	-	-	-	-	-	-	-	I 45.3	-	-	-
	2415	-	-	-	-	-	-	-	I 50.0	-	-	-	-	-	-	-
	2420	-	-	-	-	-	-	-	√ 68.1	√ 76.1	√ 70.8	√ 67.2	√ 85.2	√ 56.8	-	√ 81.8
Control	2170	-	-	-	√ 56.2	-										
	2454	-	-	-	-	-	-	-	-	-	√ 93.4	√ 78.3	√ 82.5	√ 68	√ 64.8	√ 79.8

Pre = preimmune testing; M = month post-challenge; √ = Positive, - = Negative; I = Inconclusive. Blacked out cells represent animals that were necropsied during the previous timepoint.

**Table S6.** IGRA PPDj  $\Delta$ OD readings from animals at 3 months post inoculation.

Group	ID	PPDj		ID	PPDj		ID	PPDj
Challenged	2149	0.369		2194	0.195		2403	0.012
	2152	2.947		2199	0.024		2404	0.315
	2154	1.817		2200	0.202		2407	0.161
	2155	0.005		2201	1.240		2408	0.439
	2158	0.248		2209	0.165		2410	0.116
	2162	0.115		2212	0.307		2412	0.193
	2164	0.087		2387	0.183		2413	0.051
	2169	0.141		2388	1.898		2415	0.148
	2176	0.222		2390	0.973		2416	0.204
	2182	0.512		2392	0.121		2420	0.411
	2183	0.072		2393	1.635		2422	0.140
	2185	0.061		2402	0.220			
	ID	PPDj		ID	PPDj		ID	PPDj
Control	2163	0.254		2218	0.011		2401	-0.010
	2168	2.636		2389	0.166		2405	0.681
	2170	0.022		2391	0.019		2406	0.398
	2172	0.148		2395	1.203		2409	0.062
	2175	0.324		2397	0.068		2425	0.191
	2213	1.377		2398	0.129		2454	0.771
	2215	0.212		2399	0.646			