SUPPLEMENTAL FIGURES

Figure 1S. Alpha diversity metrics of ceca across time. **(A)** Comparison of Observed ASVs, **(B)** Shannon diversity index and **(C)** Inverse Simpson of different groups (PBS/Vehicle Black, Low/Vehicle: Orange, High/Vehicle: Blue) separated by dpc from rarified ASV count table. Since the sample size was limited (n=2 or 3), pair-wise comparisons were not performed. Viral nasal turbinates (circle), lung (triangle) and brain (asterisk) titers of each group among their respective dpc are shown above the alpha diversity measure. Percent body weight change for each group at the respective dpc (2, 5, and 12) is shown above the viral titers. Data including body weight change and viral titers in the NT, lung and brain was adapted from Cáceres et al. 2021 (43).

Figure 2S. Alpha diversity metrics of cecum samples across time. **(A)** Comparison of Observed ASVs, **(B)** Shannon diversity index and **(C)** Inverse Simpson of infected groups (Low/Vehicle and High/Vehicle) separated by dpc from rarified ASV count table. All statistical tests were performed using Kruskal-Wallis or Wilcox-rank test for pair-wise comparisons using * = $p<0.05$; ** = $p<0.005$; *** = $p<0.0005$; **** = $p<0.00005$.

Figure 3S. Alpha diversity metrics of lung samples across time. **(A)** Comparison of Observed ASVs, **(B)** Shannon diversity index and **(C)** Inverse Simpson of different groups (Mock/GC-376: Brown, Low/GC-376: Green, High/GC-376: Pink) separated by dpc from rarified ASV count table. Since the sample size was limited (n=2 or 3) pair-wise comparisons were not performed. Viral nasal turbinates (circle), lung (triangle) and brain (asterisk) titers of each group among their respective dpc are shown above the alpha diversity measure. Percent body weight change for each group at the respective dpc (2 , 5, and 12 dpc) is shown above the viral titers. Data including body weight change and viral titers in the NT, lung and brain was adapted from Cáceres et al. 2021 (43).

Figure 4S. Alpha diversity metrics of lung samples across time. **(A)** Comparison of Observed ASVs, **(B)** Shannon diversity index and **(C)** Inverse Simpson of infected groups (Low/GC-376 and High/GC-376) separated by dpc from rarified ASV count table. All statistical tests were performed using Kruskal-Wallis or Wilcox-rank test for pair-wise comparisons using * = $p<0.05$; ** = $p<0.005$; *** = $p<0.0005$; **** = $p<0.00005$.

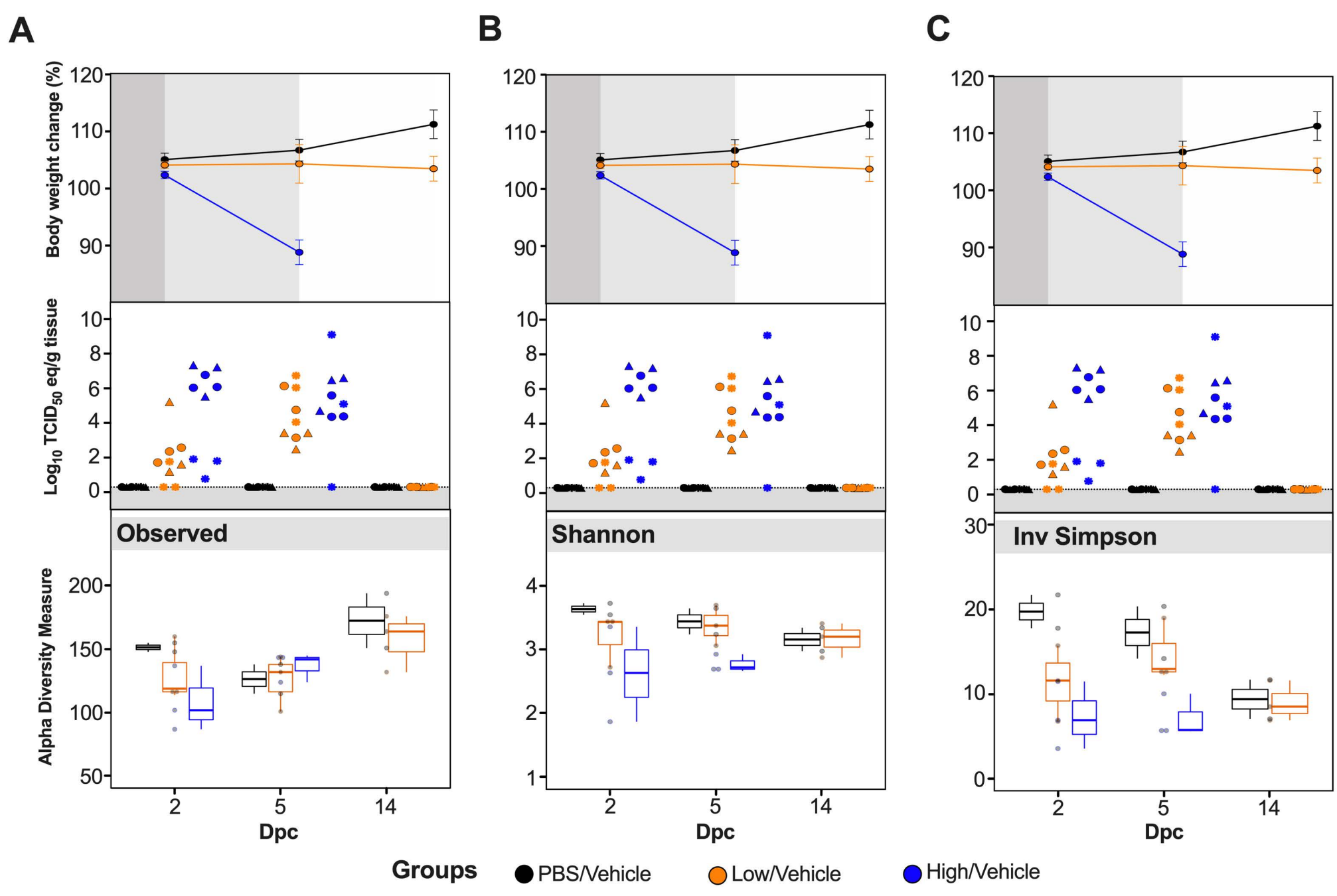
Figure 5S. Bray-Curtis Dissimilarity distances of lung samples without / with antiviral GC-376. Comparison of Bray-Curtis dissimilarity distances of mice infected with a A) low dose or (B) high dose of SARS-CoV-2 with or without GC-376. Gold boxes represent within-group variation while black boxes represent the between-group variation.

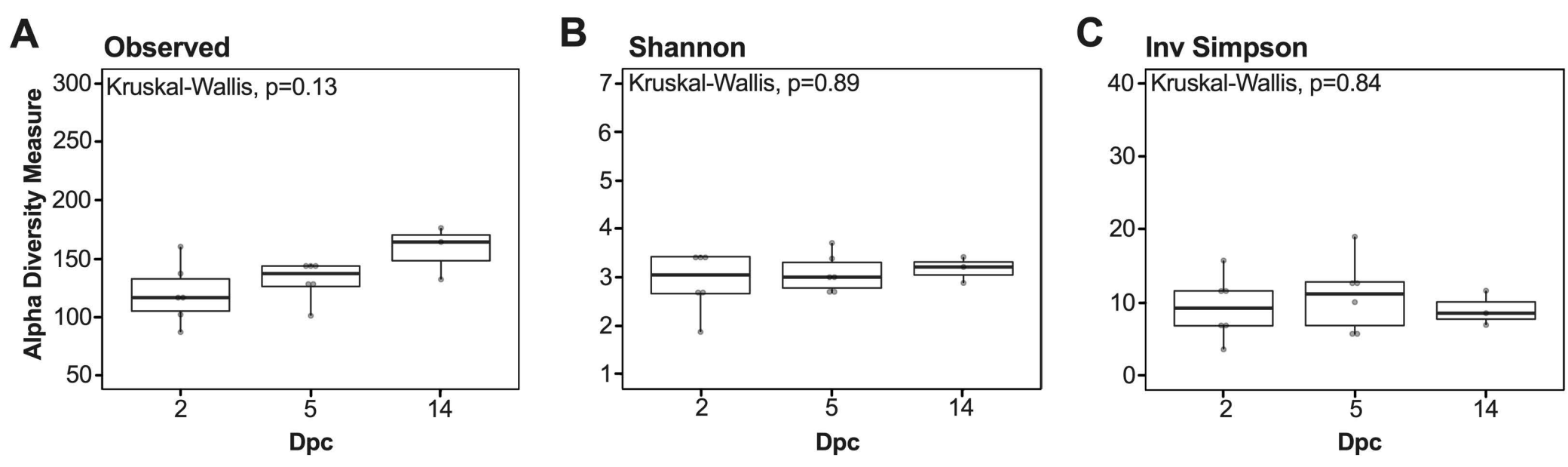
TABLE S1

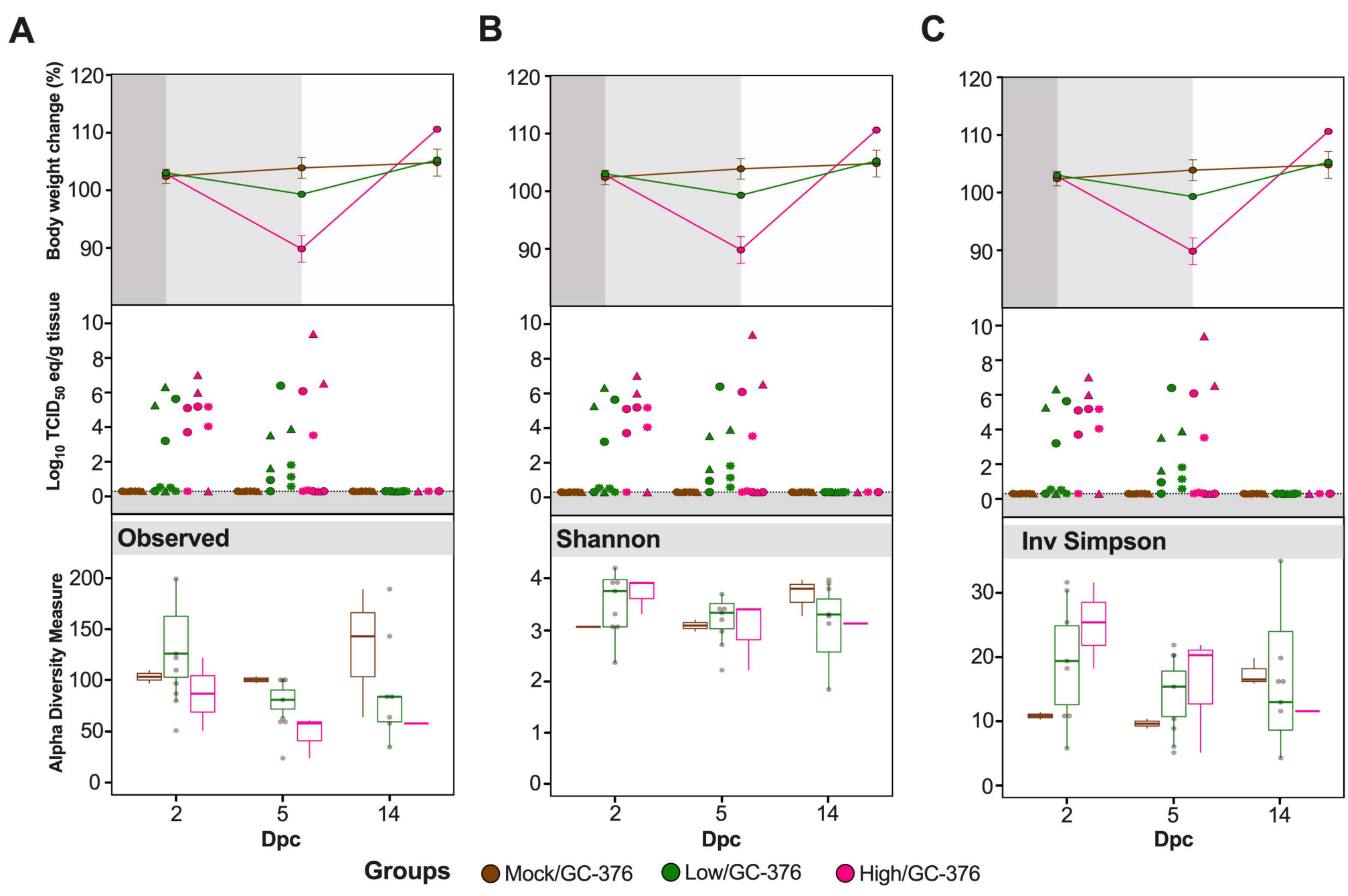
Identification of Potential Contaminants by Decontam

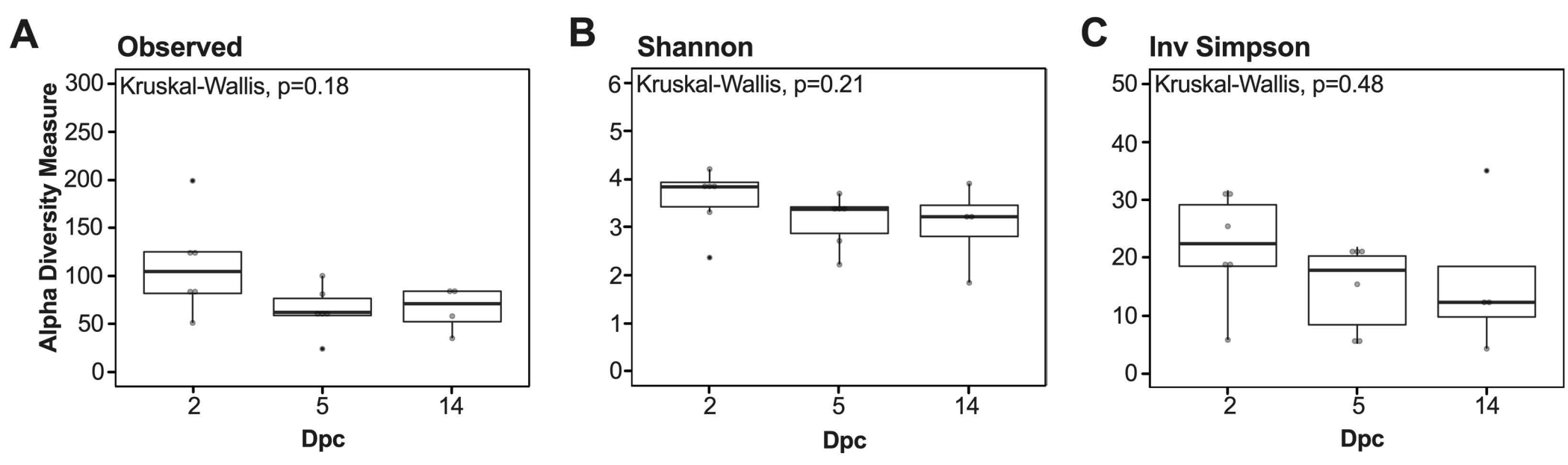
ASV ID	Kingdom	Phylum	Class	Order	Family	Genus
ASV_249	Bacteria	Firmicutes	Clostridia	Oscillospirales	Oscillospiraceae	Colidextribacter
ASV_314	Bacteria	Bacteroidota	Bacteroidia	Flavobacteriales	Weeksellaceae	Empedobacter
ASV_355	Bacteria	Firmicutes	Bacilli	Lactobacillales	Vagococcaceae	Vagococcus
ASV_395	Bacteria	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Moraxellaceae	Acinetobacter
ASV_398	Bacteria	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Moraxellaceae	Acinetobacter
ASV_470	Bacteria	Proteobacteria	Alphaproteobacteria	Rhodobacterales	Rhodobacteraceae	Gemmobacter
ASV_522	Bacteria	Firmicutes	Clostridia	Oscillospirales	Oscillospiraceae	NA
ASV_635	Bacteria	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Moraxellaceae	Acinetobacter
ASV_680	Bacteria	Proteobacteria	Alphaproteobacteria	Sphingomonadales	Sphingomonadaceae	Sphingomonas
ASV_714	Bacteria	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	Lactococcus

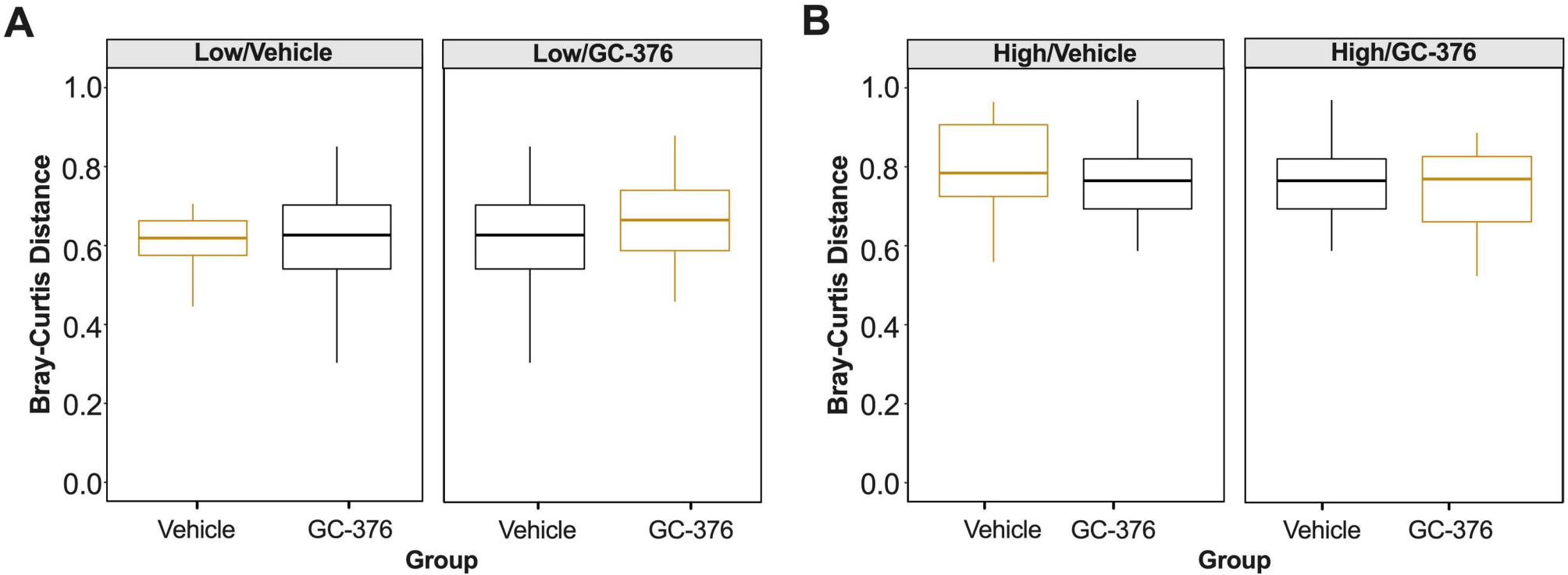
ASV_725	Bacteria	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Pseudomonadaceae	Pseudomonas
ASV_739	Bacteria	Proteobacteria	Gammaproteobacteria	Burkholderiales	Comamonadaceae	NA
ASV_761	Bacteria	Firmicutes	Clostridia	Oscillospirales	Oscillospiraceae	Flavonifractor
ASV_865	Bacteria	Firmicutes	Clostridia	Lachnospirales	Lachnospiraceae	NA


A
B
C
Body weight change (%)
120
110
100
90
Log10 TCID50 eq/g tissue
10
8
6
4
2
0
Alpha Diversity Measure
Observed
200
150
100
50
Shannon
4
3
2
1
Inv Simpson
30
20
10
0
2
5
14
Dpc
Groups
PBS/Vehicle
Low/Vehicle
High/Vehicle


A
Observed
Kruskal-Wallis, p=0.13
Alpha Diversity Measure
300
250
200
150
100
50
2
5
14
Dpc
B
Shannon
Kruskal-Wallis, p=0.89
7
6
5
4
3
2
1
2
5
14
Dpc
C
Inv Simpson
Kruskal-Wallis, p=0.84
40
30
20
10
0
2
5
14
Dpc


A
B
C
Body weight change (%)
120
110
100
90
Log10 TCID50 eq/g tissue
10
8
6
4
2
0
Alpha Diversity Measure
Observed
200
150
100
50
0
Shannon
4
3
2
1
0
Inv Simpson
30
20
10
0
2
5
14
Dpc
Groups
Mock/GC-376
Low/GC-376
High/GC-376


A
Observed
Kruskal-Wallis, p=0.18
Alpha Diversity Measure
300
250
200
150
100
50
0
2
5
14
Dpc
B
Shannon
Kruskal-Wallis, p=0.21
6
5
4
3
2
1
0
2
5
14
Dpc
C
Inv Simpson
Kruskal-Wallis, p=0.48
50
40
30
20
10
0
2
5
14
Dpc


A
Low/Vehicle
Low/GC-376
Bray-Curtis Distance
1.0
0.8
0.6
0.4
0.2
0.0
Vehicle
GC-376
Vehicle
GC-376
Group
B
High/Vehicle
High/GC-376
Bray-Curtis Distance
1.0
0.8
0.6
0.4
0.2
0.0
Vehicle
GC-376
Vehicle
GC-376
Group