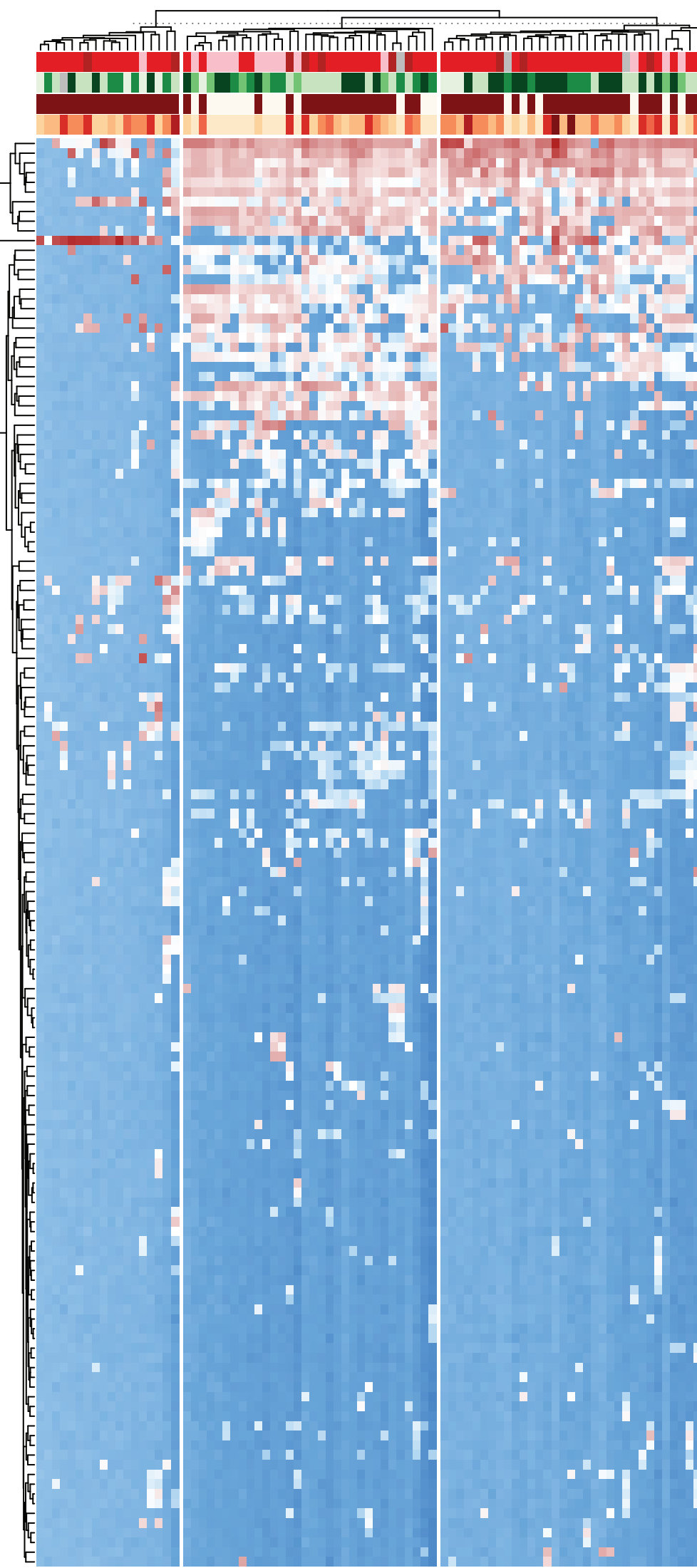


3

1

2



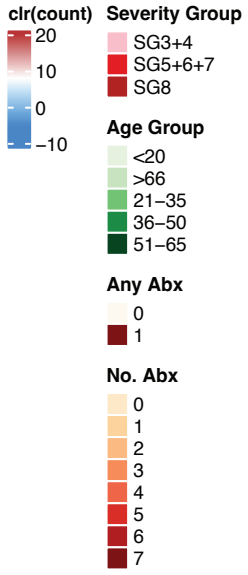
Severity Group

Age Group

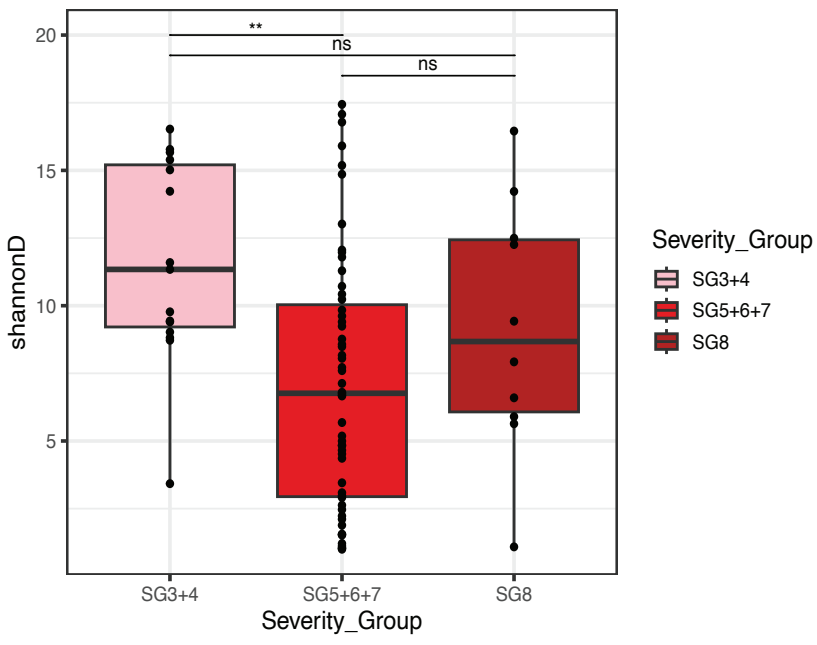
Any Abx

No. Abx

- Bacteroides
- Clostridium
- Ruminococcus
- Blautia
- Ruminococcus
- Eubacterium
- Streptococcus
- Faecalibacterium
- Alistipes
- Parabacteroides
- Enterococcus
- Lachnospirillum
- Eggerthella
- Flavonifractor
- Subdoligranulum
- Roseburia
- Dorea
- Coprococcus
- Bifidobacterium
- Lactobacillus
- Gemmiger
- Eubacterium
- Odoribacter
- Butyrivibrio
- Holdemania
- Blifilium
- Collinsella
- Sutterella
- Barnesiella
- Prevotella
- Turricoccus
- Desulfotomaculum
- Senegalimassilia
- Stactobacterium
- Olsenella
- Oscillibacter
- Parasutterella
- Akkermansia
- Dialister
- Haemophilus
- Mannheimia
- Tyzzerella
- Enterorhabdus
- Phascolarctobacterium
- Pseudobutyrvibrio
- Veillonella
- Lactococcus
- Actinomyces
- Granulicatella
- Rothia
- Leuconostoc
- Corynebacterium
- Paraprevotella
- Staphylococcus
- Tannerella
- Coprobacter
- Anaerostipes
- Enterobacter
- Raoultella
- Citrobacter
- Serratia
- Klebsiella
- Escherichia/Shigella
- Trabulsilla
- Escherichia
- Cronobacter
- Salmonella
- Pseudoflavonifractor
- Anaerotruncus
- Gordonibacter
- Adlercreutzia
- Herbaspirillum
- Ruminoclostridium
- Butyrivibrio
- Catenibacterium
- Megasphaera
- Atopobium
- Gemella
- Mogibacterium
- Howardella
- Allisonella
- Faecalicoccus
- Oribacterium
- Propionibacterium
- Abiotrophia
- Leptotrichia
- Lachnoanaerobaculum
- Acidaminococcus
- Pluralibacter
- Alloprevotella
- Prevotella
- Campylobacter
- Mitsuokella
- Bulleidia
- Succinivibrio
- Pseudomonas
- Faecalitalea
- Christensenella
- Enorma
- Lachnobacterium
- Helicobacter
- Coprobacillus
- Victivallis
- Terrisporobacter
- Fusobacterium
- Negativicoccus
- Yokenella
- Acetivibrio
- Varibaculum
- Aggregatibacter
- Parvimonas
- Peptostreptococcus
- Actinobaculum
- Arthrobacter
- Balstonia
- Peptoniphilus
- Bacillus
- Burkholderia
- Anaerofilum
- Methanobrevibacter
- Robinsonella
- Romboutsia
- Gardnerella
- Parasporobacterium
- Mangrovibacter
- Anaeroglobus
- Carnobacterium
- Pediococcus
- Parvibacter
- Denitrobacterium
- Moryella
- Hafnia
- Oxalobacter
- Cloacibacillus
- Synergistes
- Acetanaerobacterium
- Scardovia
- Morganella
- Providencia
- Kluyvera
- Yersinia
- Lactonifractor
- Fingoldia
- Alloscardovia
- Acetatifactor
- Erysipelatoclostridium
- Megamonas



A

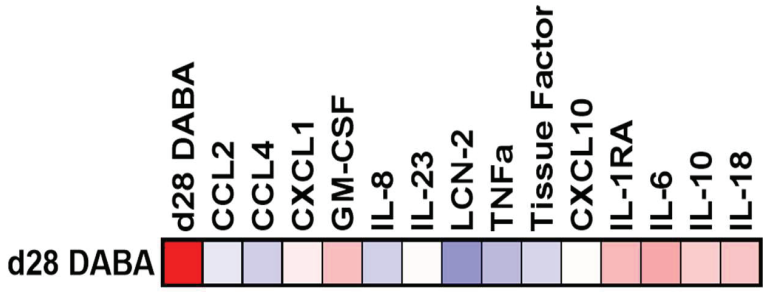


B

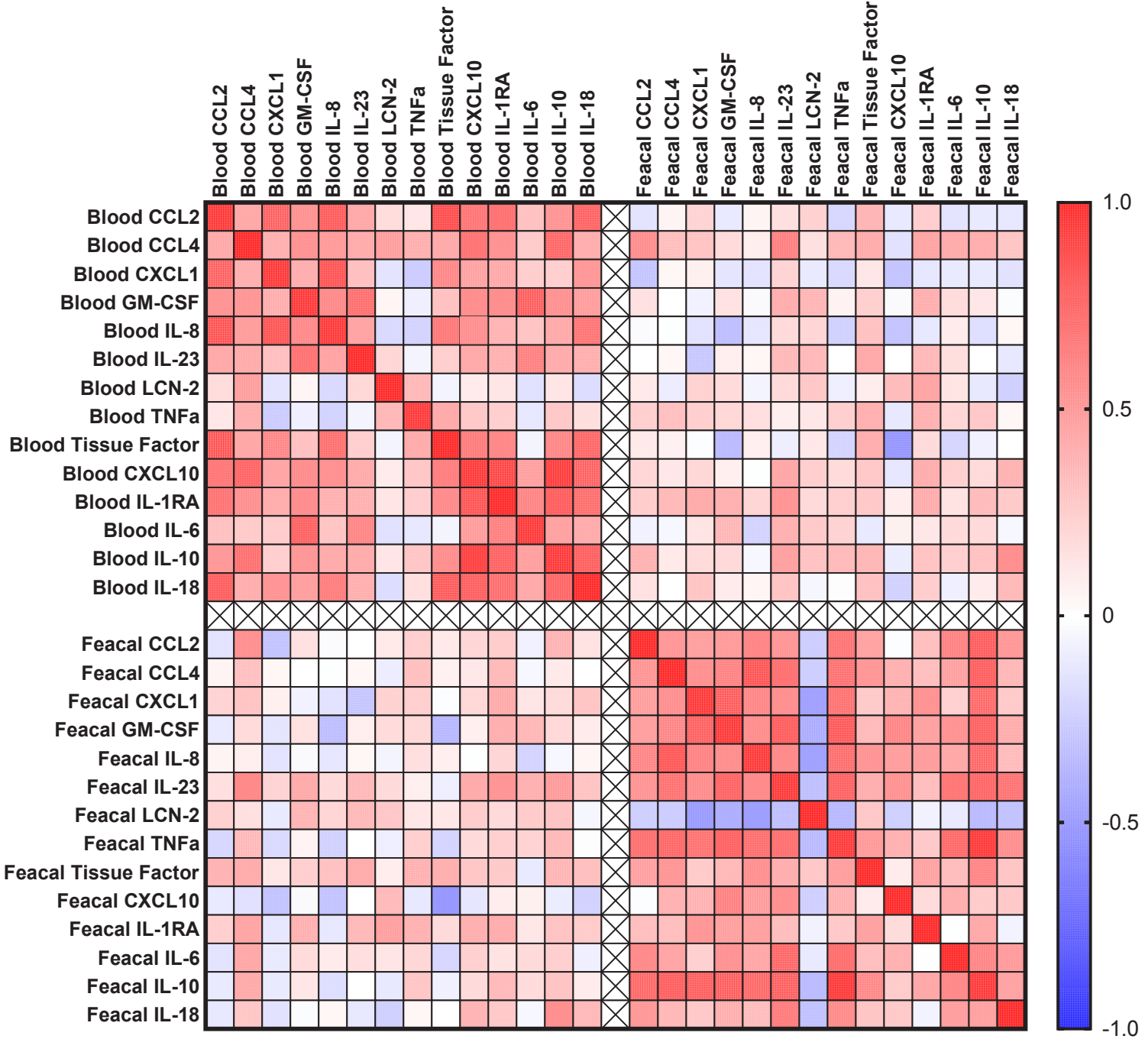
Severity Group	Number of Antibiotics	
	0	1
3+4	12	3
5+6+7	5	50
8	1	9

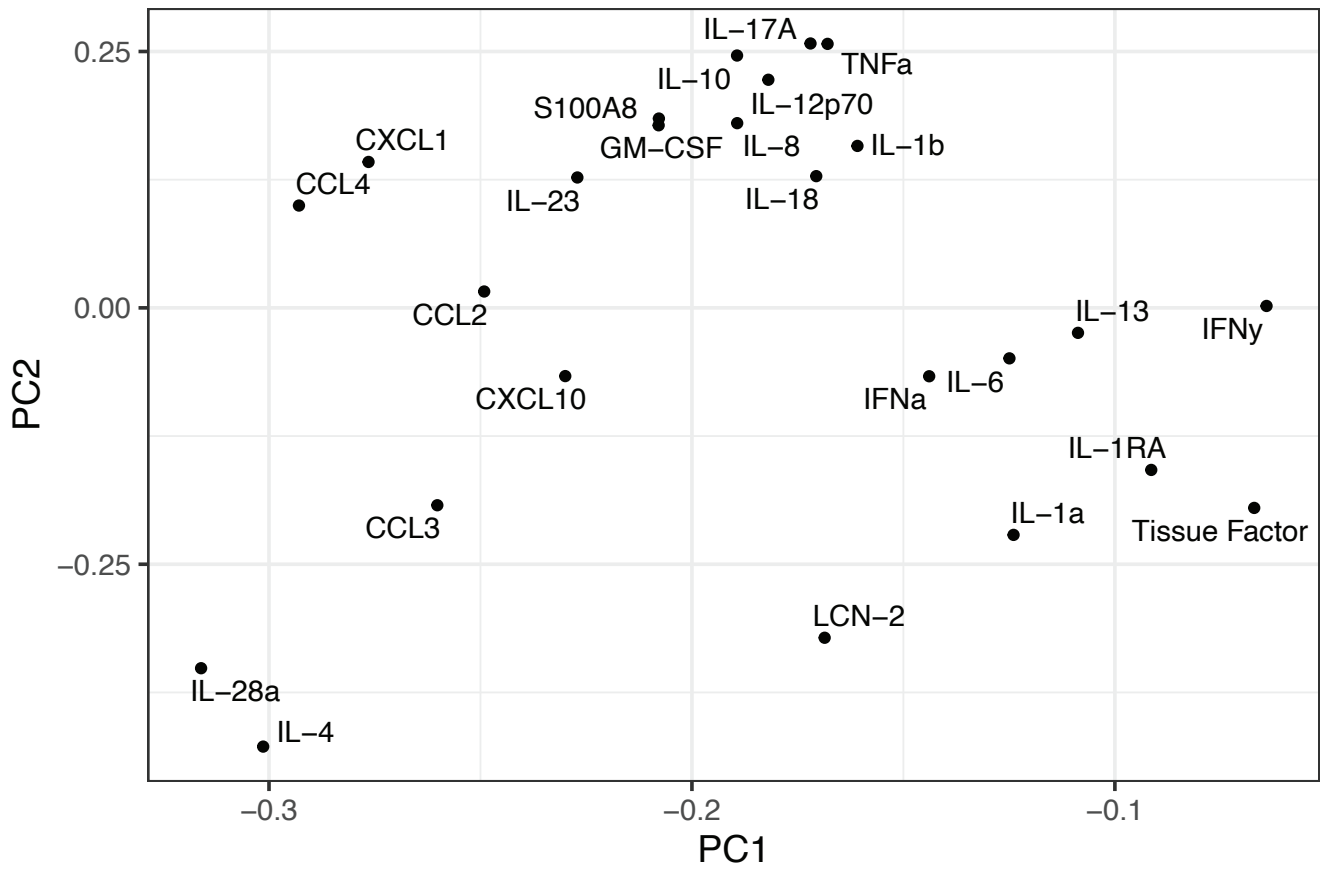
Fisher's Exact Test  $p = 2.18 \times 10^{-7}$

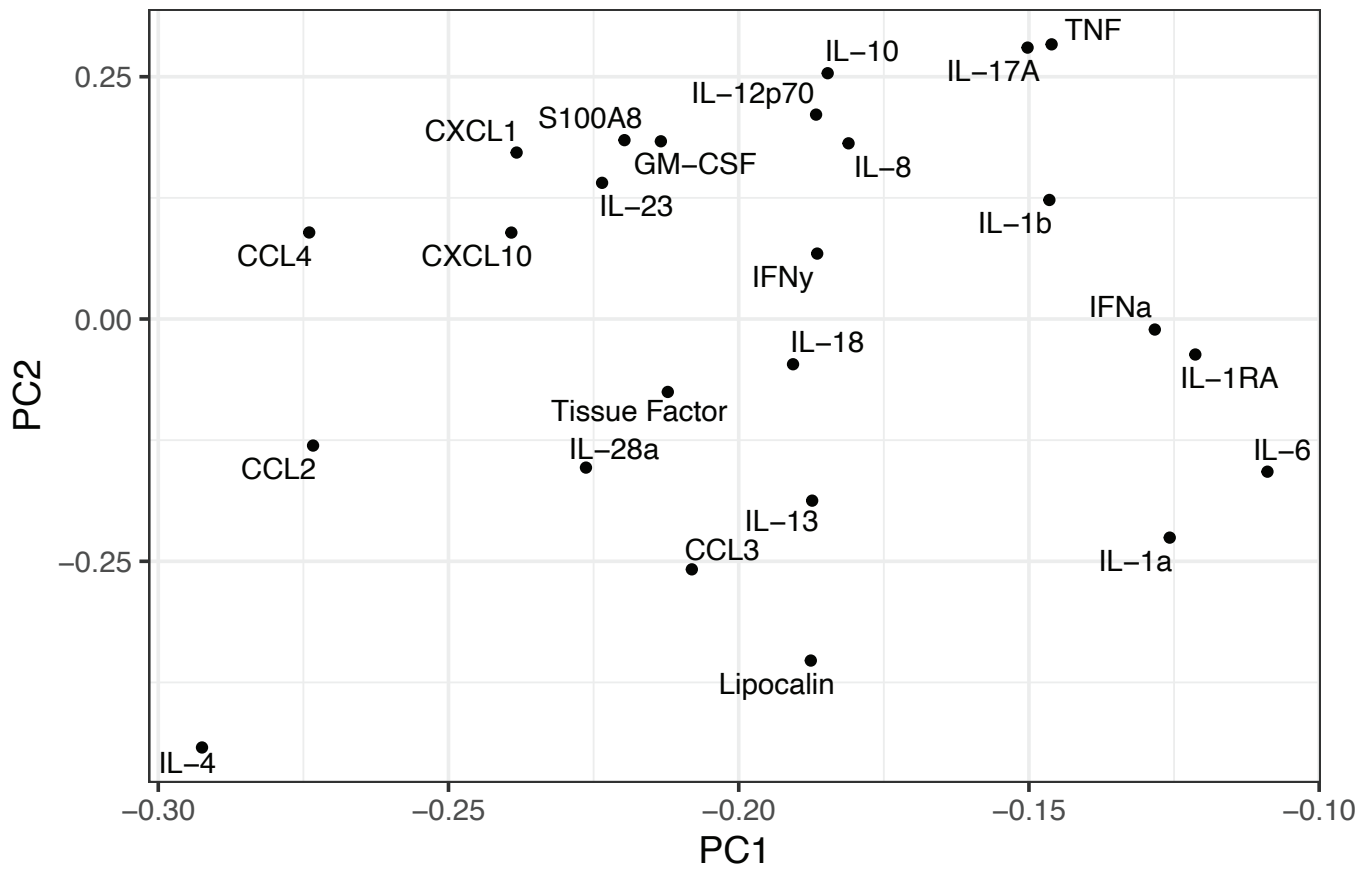
A



B







	<b>Df</b>	<b>Sum Of Sqs</b>	<b>R2</b>	<b>F</b>	<b>p value</b>	<b>p value (adjusted)</b>
D28 DABA	1	14.795	0.027	0.870	0.529	0.529
Peak SASS	1	43.270	0.071	2.757	0.014	0.084
Log10 (Peak URT VL)	1	31.230	0.051	1.948	0.046	0.092
Peak GISS	1	14.730	0.024	0.893	0.483	0.529
D7 URT VL	1	61.778	0.106	4.048	0.033	0.092
D7 Faecal VL	1	32.948	0.054	2.062	0.090	0.135



## **Supplementary Figure Legends**

**Supplementary Figure 1: Mild COVID-19 cases have a pronounced proinflammatory gut mucosal cytokine response compared to uninfected controls and patients with severe COVID-19 disease.** Heatmap of Z-scored faecal cytokine concentrations in D7 samples from INSTINCT study participants and D0 (time of enrolment) samples from ISARIC participants grouped according to severity group. Row annotations show concomitant (D7) upper respiratory tract (URT) and faecal viral load measurements vaccination status at the time of enrolment. All vaccinated participants received a single dose of either Pfizer or Oxford/Astra Zeneca COVID-19 vaccination.

**Supplementary Figure 2: Mild COVID-19 cases (n=45) have a pronounced proinflammatory gut mucosal cytokine response.** Concentrations of 17 cytokines in faecal samples stratified by severity groups. Results of Kruskal Wallis tests with Dunn's multiple comparison tests are displayed\*  $p < 0.05$ , \*\* $p < 0.01$ , \*\*\*  $p < 0.001$ , \*\*\*\*  $p < 0.0001$ .

**Supplementary Figure 3: Heatmap of microbiome at the genus level.** Hierarchical clustering of sequenced microbiome (n=83) annotated with severity group, age group, qualitative and quantitative antibiotic data.

**Supplementary Figure 4: Antibiotic usage confounds microbiome data. A.** Alpha diversity of the microbiome sequences by Shannon D index according to severity group. **B.** Contingency table showing how many people were taking antibiotics (0 = no antibiotic use, 1 = used at least one antibiotic) in each severity group.

**Supplementary Figure 5: Serum cytokines do not correlate with D28 DABA or faecal cytokines. A.** Correlation matrix between serum cytokines and D28 DABA measurements. **B.** Correlation matrix between faecal and serum cytokines.

**Supplementary Figure 6:** Loading plot for PCA analysis represented in Figure 2B showing faecal cytokine concentration in PCR-positive cases (n=88) ranging from severity groups 1 to 8.

**Supplementary Figure 7:** Loading plot for PCA analysis represented in Figure 4F showing faecal cytokine concentration in mild PCR+ cases at day 7 (n=45) and day 28 (n=38), and in PCR- cases (n=12).

**Supplementary Table 1:** PERMANOVA of faecal cytokines from PCR+ cases at day 28 (n=38) against day 28 DABA levels, peak SASS, peak GISS, log<sub>10</sub> of peak viral load (VL) in URT, faecal viral load at day 28. And URT viral load at day 28.

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**Highlights:**

- SARS-CoV-2 viral load trajectories in the upper respiratory tract and gut are non-correlated
- A transient gut cytokine signature is associated with increased systemic antibody responses to SARS-CoV-2
- In hospitalised patients, production of gut cytokines comprising the aforementioned signature associates with favourable clinical outcomes