

Supplementary Table S1. Bacterial strains

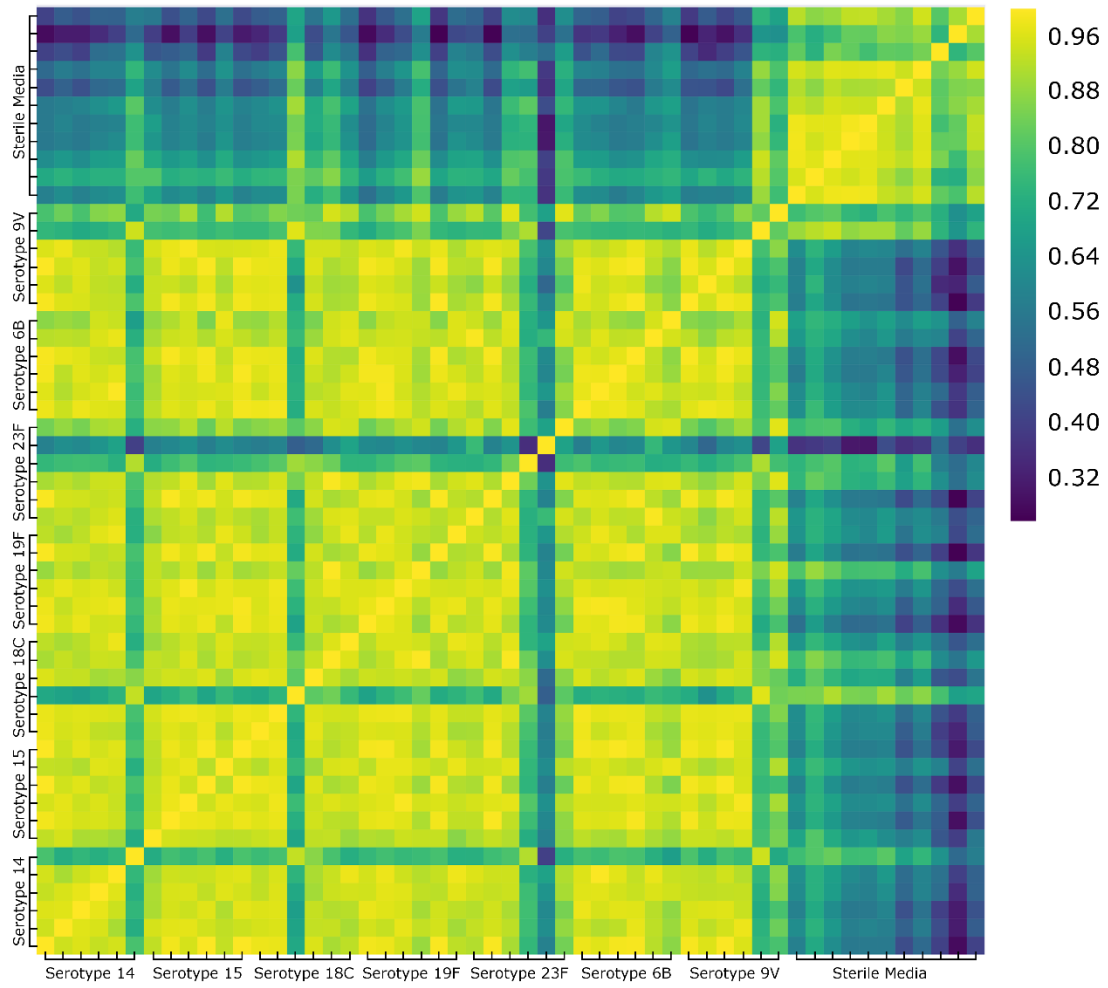
Recipient			Donor			Capsule switch mutant		
Strain	Serotype	Capsule size (bp)	Strain	Serotype	Capsule size (bp)	Mutant	Serotype	Total samples prepared
106.66	6B	17506	NA	NA	NA	NA	6B	3
106.66	6B	17506	106.66	6B	17506	106.66cps106.66	6B	3
106.66	6B	17506	B101.77	14	19918	106.66cpsB101.77	14	6
106.66	6B	17506	201.38	9V	20856	106.66cps201.38	9V	3
106.66	6B	17506	109.74	9V	20856	106.66cps109.74	9V	3
106.66	6B	17506	207.31	15	18626	106.66cps207.31	15	6
106.66	6B	17506	307.14	18C	21819	106.66cps307.14	18C	6
106.66	6B	17506	103.57	23F	22330	106.66cps103.57	23F	6
106.66	6B	17506	108.34	19F	19798	106.66cps108.34	19F	2
106.66	6B	17506	201.47	19F	19798	106.66cps201.47	19F	2
106.66	6B	17506	B201.73	19F	19798	106.66cpsB201.73	19F	2

Supplementary Table S2. Modified lacks medium reagents, modified from [1]

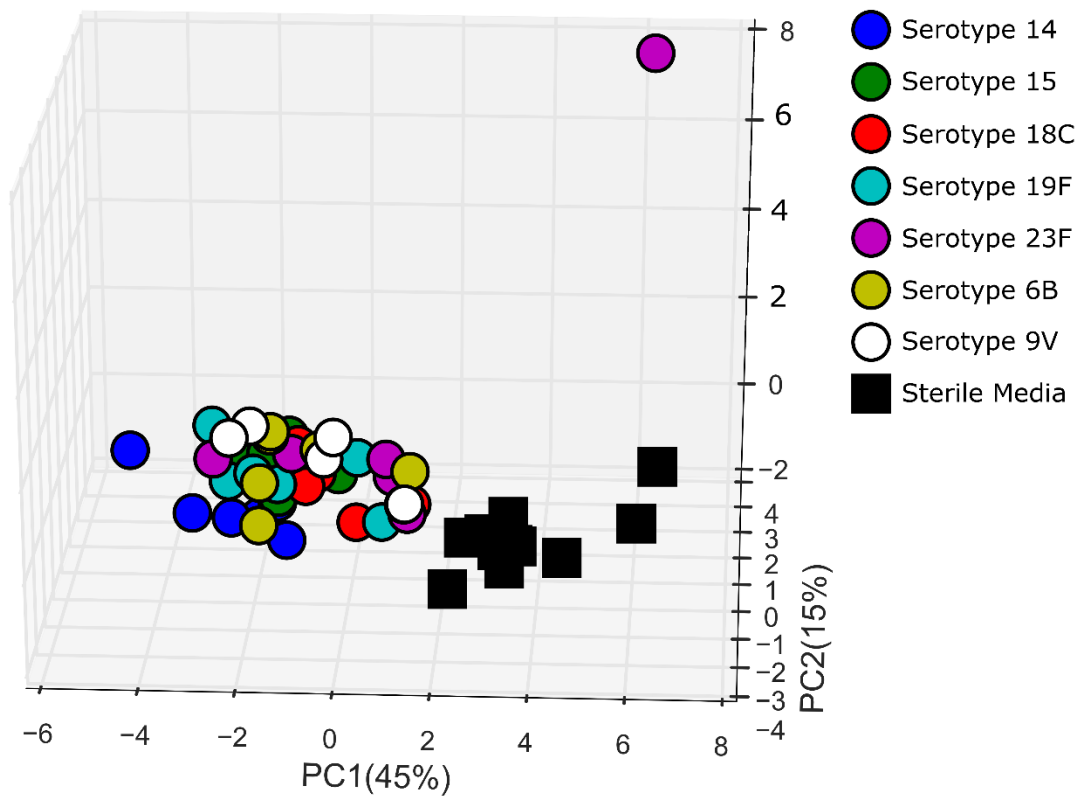
Component	Amount/liter
casamino acids	1.25 g
casein hydrolysate	0.25 g
tryptophan	1.5 mg
cysteine HCl	10 mg
asparagine	12.5 mg
glutamine	2.5 mg
choline HCl	5 mg
adenine	5 mg
sodium acetate	2 g
K ₂ HPO ₄	8.5 g
MgCl ₂ · 6 H ₂ O	0.5 g
CaCl ₂	0.6 mg
MnSO ₄ · 4 H ₂ O	0.2 mg
FeSO ₄ · 7 H ₂ O	0.5 mg
CuSO ₄ · 5 H ₂ O	0.5 mg
ZnSO ₄ · 7 H ₂ O	0.5 mg
NaHCO ₃	0.4 g
Biotin	0.6 µg
nicotinic acid	0.3 mg
pyridoxine·HCl	0.3 mg
thiamine·HCl	0.3 mg
Riboflavin	0.14 mg
calcium pantothenate	1.2 mg
Sucrose	3.423 g
catalase from bovine liver (Sigma)	12000 units

pH

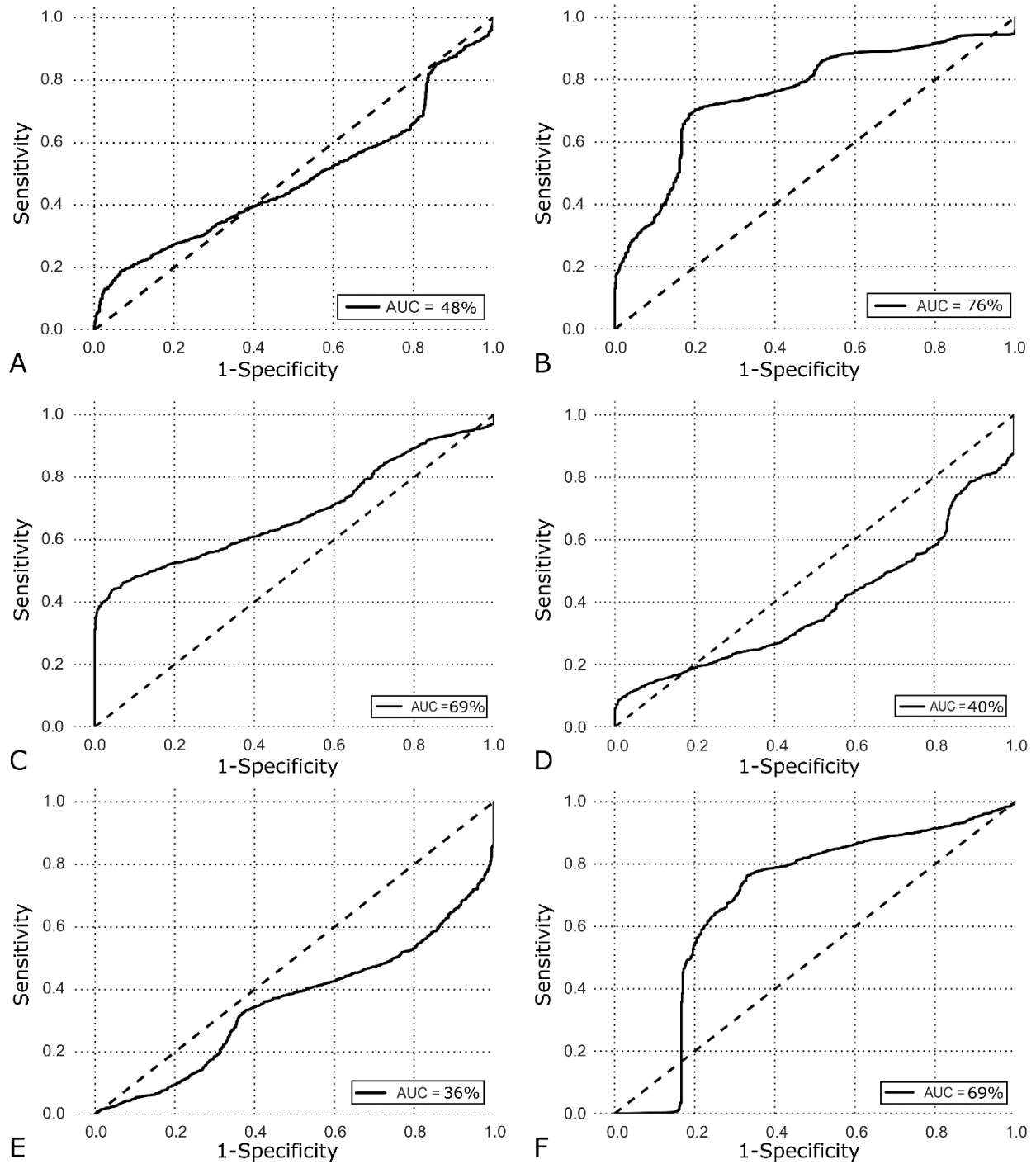
adjusted to 7.3



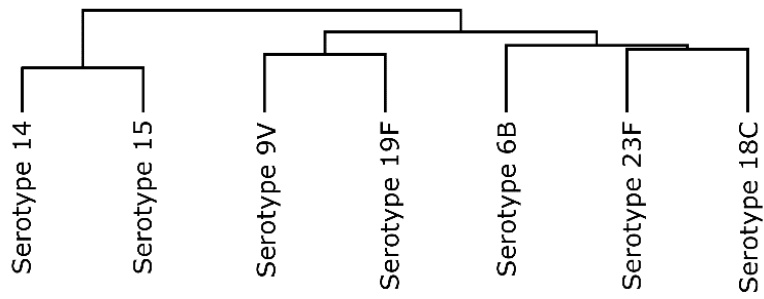
Supplementary Figure S1. Spearman's rank correlation between samples when considering the 13 core molecules found to be statistically different between the aggregated *S. pneumoniae* cultures and sterile media.



Supplementary Figure S2. Principal component analysis (PCA) of *S. pneumoniae* culture and sterile media samples when considering the 13 statistically significant molecules. Strep samples are labeled by serotype.



Supplementary Figure S3. Receiver operating characteristic (ROC) curve showing the discriminatory efficacy for differentiating A) serotype 23F from serotypes 14, 15, 18C, 19F, 9V and 6B; B) Serotype 15 from serotypes 14, 23F, 18C, 19F, 9V and 6B; C) serotype 6B from serotypes 14, 23F, 15, 18C, 19F and 9V; D) serotype 19F from serotypes 14, 23F, 15, 18C, 9V and 6B; E) serotype 9V from serotypes 14, 15, 18C, 19F, 23F and 6B; F) serotype 18C from serotypes 14, 15, 23F, 19F, 9V and 6B.



Supplementary Figure S4. Hierarchical clustering analysis of *S. pneumoniae* capsular polysaccharide locus based on the presence and absence of capsule genes for serotypes 14, 15, 6B, 9V, 18C, 19F and 23F.

References

1. Lacks, S., *Integration efficiency and genetic recombination in pneumococcal transformation*. *Genetics*, 1966. **53**(1): p. 207.