## Supplementary Tables

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						om Conc	tio Bogie				1			
A	Strain	1	2	3	2 4 A	5	6	7	8	9	Methyltransferase	Type	Serotype	Sequence Type
	310	1 1>	1.2>	PsrA>	2.3>	<22	<11		Ů	3	<m< td=""><td>3</td><td>24F</td><td>11618</td></m<>	3	24F	11618
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	525	1.1>	2.1>	PsrA>	2.3>	<2.2	<1.1				<m< td=""><td>1</td><td>24F</td><td>15253</td></m<>	1	24F	15253
	563	1.2>	2.1>	PsrA>	2.2>	<2.3	<1.1				<m< td=""><td>1</td><td>24F</td><td>15253</td></m<>	1	24F	15253
	566	1.1>	2.1>	PsrA>	2.3>	?	<1.2				<m< td=""><td>1</td><td>24F</td><td>11618</td></m<>	1	24F	11618
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	A66												3	378
	AP200	12~	22~	<23	<psr<sup>Δ</psr<sup>	<21	<11				٢M	1	11A	62
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	ATCC 49619	1.2>	2.1>	PsrA>	2.3>	<2.2	<1.1				<m< td=""><td>1</td><td>19F</td><td>1203</td></m<>	1	19F	1203
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	R6CIB17	1.2>	2.2>	<2.3	<psra< td=""><td>&lt;2.1</td><td>&lt;1.1</td><td></td><td></td><td></td><td><m></m></td><td>1</td><td>NE</td><td>595</td></psra<>	<2.1	<1.1				<m></m>	1	NE	595
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	SWU02 Taiwar10E 14	1.1>	2.1>	rsrA>	2.2>	<2.3	<1.2				<1V1	1	19F	unidentified
	TCH8/31/10A	1.2>	2.2>	<2.3	<1.1 2.2~	-2.2	<i>c</i> 11			<u> </u>	<ivi< td=""><td>∠ 1</td><td>195</td><td>230</td></ivi<>	∠ 1	195	230
	TIGR4: ATCC BAA-334	1.2>	2.1>	PsrA>	2.3>	<2.2	<1.1				<m< td=""><td>1</td><td>13A 4</td><td>205</td></m<>	1	13A 4	205

Xen35

Γ

1.2> 2.1> **PsrA>** 2.3> <2.2 <1.1

<M

1

4

205

SpnIII Type	Prevalence in Genomes
1	68.3%
2	8.5%
3	18.3%
4	2.4%
5	6.1%
Two SpnIII Systems	6.1%
Absent	2.4%

**Supplementary Table 1.** SpnIII systems in fully annotated NCBI *S. pneumoniae* genomes. **A)** Orientation and genetic features of SpnIII systems. Direction of each feature indicated with either > or <. *hsdS* sequences 1.1, 1.2, 2.1, 2.2 and 2.3 included. **Red** highlighted sections have low (<80%) sequence identity to known *hsdS* sequences. "?" indicates a *hsdS* region with an identity <50% to the known *hsdS* sequences. Duplications of features are indicated in **Green**. The CreX recombinase – Pneumococccal site-specific recombinase A (PsrA) included in **Bold**. The sequence for the associated Methyltransferase (M) was also included with orientation. Serotype and Sequence Type information for each strain have been included where available. \*NA indicates the strain contains 6 of 7 MLST genes, and NE indicates the strain is non-encapsulated. The prevalence of each major type of SpnIII system found in genomes can be seen in **B**). Type 1 is the 'traditional' six-way switch as seen in **Figure 1A**. Type 2, seen in **Figure 1B**, is a four-way switch. Type 3 is a three-way switch as per **Figure 1C**. Type 4 is a two-way switch, as per **Figure 1D**. Type 5 were instances that did not fall into the previous four categories.

Α	Protein Antigen Expression in D39									
Allele	CbpA	GlpO	MalX	NanA	NanB	PhtD	PiuA	Ply	PsaA	PspA
Α										
В	-2.0	-5.0	-6.1	-20.2	-2.9	-3.3	-1.6	1.6	-3.9	-3.2
С	-3.4	-6.6	-3.7	-26.2	-8.2	-7.3	-3.7	-1.1	-7.2	-4.4
D	-2.4	-1.6	-4.1	-12.8	-4.9	-3.6	-7.0	1.1	-2.4	-2.5
E	-2.7	-3.8	-4.0	-16.6	-7.4	-6.3	-4.4	-1.0	-4.7	-4.9
F	2.0	2.4	-1.1	1.4	-3.5	1.2	1.1	1.5	1.3	1.3
Allele	CbpA	GlpO	MalX	NanA	NanB	PhtD	PiuA	Ply	PsaA	PspA
A	2.0	5.0	6.1	20.2	2.9	3.3	1.6	-1.6	3.9	3.2
В	47	1.0		1.0	0.0		0.4	1.0	1.0	
C	-1./	-1.3	1.6	-1.3	-2.8	-2.2	-2.4	-1.8	-1.8	-1.4
	-1.2	3.0	1.5	1.6	-1.7	-1.1	-4.5	-1.5	1.7	1.3
E	-1.4	1.3	1.5	1.2	-2.5	-1.9	-2.8	-1.7	-1.2	-1.5
F	4.0	11.8	5.6	27.8	-1.2	4.0	1.8	-1.1	5.0	4.3
Allolo	ChnA	GlnO	MalX	NanA	NanB	PhtD	DiuA	Dhy	Dea A	PenA
	3.4	66	3.7	26.2	8.2	73	37	11	72	
B	17	1.3	-1.6	13	2.8	2.2	2.4	1.1	1.2	4.4 1 /
<u>с</u>	1.7	1.5	-1.0	1.5	2.0	2.2	2.4	1.0	1.0	1.4
	14	4.0	_1 1	21	17	2.0	-19	12	3.0	1.8
F	13	1.8	_1.1	1.6	1.7	1.2	-1.3	1.2	1.5	-1 1
F	6.8	15.8	34	36.0	24	8.7	4.2	1.1	9.1	59
	0.0	10.0	0.4	00.0	<b>2</b> .न	0.1	٦.٢	1.7	0.1	0.0
Allele	CbpA	GlpO	MalX	NanA	NanB	PhtD	PiuA	Ply	PsaA	PspA
Α	2.4	1.6	4.1	12.8	4.9	3.6	7.0	-1.1	2.4	2.5
В	1.2	-3.0	-1.5	-1.6	1.7	1.1	4.5	1.5	-1.7	-1.3
С	-1.4	-4.0	1.1	-2.1	-1.7	-2.0	1.9	-1.2	-3.0	-1.8
D										
E										
	-1.1	-2.3	1.0	-1.3	-1.5	-1.7	1.6	-1.1	-2.0	-2.0
F	-1.1 4.8	<mark>-2.3</mark> 3.9	1.0 3.8	-1.3 17.6	<mark>-1.5</mark> 1.4	-1.7 4.3	1.6 8.1	<mark>-1.1</mark> 1.4	-2.0 3.0	<mark>-2.0</mark> 3.3
F	-1.1 4.8	<mark>-2.3</mark> 3.9	1.0 3.8	-1.3 17.6	<mark>-1.5</mark> 1.4	<mark>-1.7</mark> 4.3	1.6 8.1	<mark>-1.1</mark> 1.4	<mark>-2.0</mark> 3.0	-2.0 3.3
F Allele	-1.1 4.8 CbpA	-2.3 3.9 GlpO	1.0 3.8 MalX	-1.3 17.6 NanA	-1.5 1.4 NanB	-1.7 4.3 PhtD	1.6 8.1 PiuA	-1.1 1.4 Ply	-2.0 3.0 PsaA	-2.0 3.3 PspA
F Allele A	-1.1 4.8 <b>CbpA</b> 2.7	-2.3 3.9 GlpO 3.8	1.0 3.8 <b>MalX</b> 4.0	-1.3 17.6 NanA 16.6	-1.5 1.4 NanB 7.4	-1.7 4.3 PhtD 6.3	1.6 8.1 PiuA 4.4	-1.1 1.4 <b>Ply</b> 1.0	-2.0 3.0 PsaA 4.7	-2.0 3.3 PspA 4.9
F Allele A B	-1.1 4.8 <b>CbpA</b> 2.7 1.4	-2.3 3.9 GlpO 3.8 -1.3	1.0 3.8 MalX 4.0 -1.5	-1.3 17.6 NanA 16.6 -1.2	-1.5 1.4 NanB 7.4 2.5	-1.7 4.3 PhtD 6.3 1.9	1.6 8.1 PiuA 4.4 2.8	-1.1 1.4 Ply 1.0 1.7	-2.0 3.0 <b>PsaA</b> 4.7 1.2	-2.0 3.3 <b>PspA</b> 4.9 1.5
F Allele A B C	-1.1 4.8 <b>CbpA</b> 2.7 1.4 -1.3	-2.3 3.9 GlpO 3.8 -1.3 -1.8	1.0 3.8 MalX 4.0 -1.5 1.1	-1.3 17.6 NanA 16.6 -1.2 -1.6	-1.5 1.4 NanB 7.4 2.5 -1.1	-1.7 4.3 PhtD 6.3 1.9 -1.2	1.6 8.1 <b>PiuA</b> 4.4 2.8 1.2	-1.1 1.4 <b>Ply</b> 1.0 1.7 -1.1	-2.0 3.0 <b>PsaA</b> 4.7 1.2 -1.5	-2.0 3.3 PspA 4.9 1.5 1.1
F Allele A B C D	-1.1 4.8 <b>CbpA</b> 2.7 1.4 -1.3 1.1	-2.3 3.9 GlpO 3.8 -1.3 -1.8 2.3	1.0 3.8 MalX 4.0 -1.5 1.1 1.0	-1.3 17.6 NanA 16.6 -1.2 -1.6 1.3	-1.5 1.4 NanB 7.4 2.5 -1.1 1.5	-1.7 4.3 PhtD 6.3 1.9 -1.2 1.7	1.6 8.1 PiuA 4.4 2.8 1.2 -1.6	-1.1 1.4 <b>Ply</b> 1.0 1.7 -1.1 1.1	-2.0 3.0 <b>PsaA</b> 4.7 1.2 -1.5 2.0	-2.0 3.3 <b>PspA</b> 4.9 1.5 1.1 2.0
F Allele A B C D E	-1.1 4.8 <b>CbpA</b> 2.7 1.4 -1.3 1.1	-2.3 3.9 GlpO 3.8 -1.3 -1.8 2.3	1.0 3.8 MalX 4.0 -1.5 1.1 1.0	-1.3 17.6 NanA 16.6 -1.2 -1.6 1.3	-1.5 1.4 NanB 7.4 2.5 -1.1 1.5	-1.7 4.3 PhtD 6.3 1.9 -1.2 1.7	1.6 8.1 PiuA 4.4 2.8 1.2 -1.6	-1.1 1.4 Ply 1.0 1.7 -1.1 1.1	-2.0 3.0 <b>PsaA</b> 4.7 1.2 -1.5 2.0	-2.0 3.3 <b>PspA</b> 4.9 1.5 1.1 2.0
F Allele A B C D E F	-1.1 4.8 <b>CbpA</b> 2.7 1.4 -1.3 1.1 5.3	-2.3 3.9 GlpO 3.8 -1.3 -1.8 2.3 9.0	1.0 3.8 MalX 4.0 -1.5 1.1 1.0 3.7	-1.3 17.6 NanA 16.6 -1.2 -1.6 1.3 22.8	-1.5 1.4 NanB 7.4 2.5 -1.1 1.5 2.1	-1.7 4.3 PhtD 6.3 1.9 -1.2 1.7 7.5	1.6 8.1 PiuA 4.4 2.8 1.2 -1.6 5.0	-1.1 1.4 Ply 1.0 1.7 -1.1 1.1 1.1	-2.0 3.0 <b>PsaA</b> 4.7 1.2 -1.5 2.0 6.0	-2.0 3.3 <b>PspA</b> 4.9 1.5 1.1 2.0 6.6
F Allele A B C D E F	-1.1 4.8 <b>CbpA</b> 2.7 1.4 -1.3 1.1 5.3	-2.3 3.9 GlpO 3.8 -1.3 -1.8 2.3 9.0	1.0 3.8 MalX 4.0 -1.5 1.1 1.0 3.7	-1.3 17.6 NanA 16.6 -1.2 -1.6 1.3 22.8	-1.5 1.4 NanB 7.4 2.5 -1.1 1.5 2.1	-1.7 4.3 PhtD 6.3 1.9 -1.2 1.7 7.5	1.6 8.1 PiuA 4.4 2.8 1.2 -1.6 5.0	-1.1 1.4 Ply 1.0 1.7 -1.1 1.1 1.6	-2.0 3.0 PsaA 4.7 1.2 -1.5 2.0 6.0	-2.0 3.3 <b>PspA</b> 4.9 1.5 1.1 2.0 6.6
F Allele A B C D E F Allele	-1.1 4.8 CbpA 2.7 1.4 -1.3 1.1 5.3 CbpA	-2.3 3.9 GlpO 3.8 -1.3 -1.8 2.3 9.0 9.0	1.0 3.8 MalX 4.0 -1.5 1.1 1.0 3.7 MalX	-1.3 17.6 NanA 16.6 -1.2 -1.6 1.3 22.8 NanA	-1.5 1.4 NanB 7.4 2.5 -1.1 1.5 2.1 2.1 NanB	-1.7 4.3 PhtD 6.3 1.9 -1.2 1.7 7.5 PhtD	1.6 8.1 PiuA 4.4 2.8 1.2 -1.6 5.0 PiuA	-1.1 1.4 Ply 1.0 1.7 -1.1 1.1 1.6 Ply	-2.0 3.0 PsaA 4.7 1.2 -1.5 2.0 6.0 PsaA	-2.0 3.3 PspA 4.9 1.5 1.1 2.0 6.6 PspA
F Allele A B C D E F Allele A	-1.1 4.8 CbpA 2.7 1.4 -1.3 1.1 5.3 CbpA -2.0	-2.3 3.9 GlpO 3.8 -1.3 -1.8 2.3 9.0 9.0 GlpO -2.4	1.0 3.8 MalX 4.0 -1.5 1.1 1.0 3.7 MalX 1.1	-1.3 17.6 NanA 16.6 -1.2 -1.6 1.3 22.8 22.8 NanA -1.4	-1.5 1.4 NanB 7.4 2.5 -1.1 1.5 2.1 2.1 NanB 3.5	-1.7 4.3 PhtD 6.3 1.9 -1.2 1.7 7.5 PhtD -1.2	1.6 8.1 PiuA 4.4 2.8 1.2 -1.6 5.0 PiuA -1.1	-1.1 1.4 Ply 1.0 1.7 -1.1 1.1 1.6 Ply -1.5	-2.0 3.0 PsaA 4.7 1.2 -1.5 2.0 6.0 6.0 PsaA -1.3	-2.0 3.3 PspA 4.9 1.5 1.1 2.0 6.6 9 spA -1.3
F Allele A B C D E F Allele A B	-1.1 4.8 CbpA 2.7 1.4 -1.3 1.1 5.3 CbpA -2.0 -4.0	-2.3 3.9 GlpO 3.8 -1.3 -1.8 2.3 9.0 9.0 GlpO -2.4 -11.8	1.0 3.8 MalX 4.0 -1.5 1.1 1.0 3.7 3.7 MalX 1.1 -5.6	-1.3 17.6 NanA 16.6 -1.2 -1.6 1.3 22.8 22.8 NanA -1.4 -1.4	-1.5 1.4 NanB 7.4 2.5 -1.1 1.5 2.1 2.1 NanB 3.5 1.2	-1.7 4.3 PhtD 6.3 1.9 -1.2 1.7 7.5 PhtD -1.2 -1.2 -4.0	1.6 8.1 PiuA 4.4 2.8 1.2 -1.6 5.0 PiuA -1.1 -1.8	-1.1 1.4 Ply 1.0 1.7 -1.1 1.1 1.6 Ply -1.5 1.1	-2.0 3.0 PsaA 4.7 1.2 -1.5 2.0 6.0 6.0 PsaA -1.3 -5.0	-2.0 3.3 PspA 4.9 1.5 1.1 2.0 6.6 6.6 PspA -1.3 -1.3
F Allele A B C D E F Allele A B C	-1.1 4.8 CbpA 2.7 1.4 -1.3 1.1 5.3 CbpA -2.0 -4.0 -6.8	-2.3 3.9 GlpO 3.8 -1.3 -1.8 2.3 9.0 9.0 GlpO -2.4 -11.8 -15.8	1.0 3.8 MalX 4.0 -1.5 1.1 1.0 3.7 MalX 1.1 -5.6 -3.4	-1.3 17.6 NanA 16.6 -1.2 -1.6 1.3 22.8 22.8 NanA -1.4 -27.8 -36.0	-1.5 1.4 NanB 7.4 2.5 -1.1 1.5 2.1 NanB 3.5 1.2 -2.4	-1.7 4.3 PhtD 6.3 1.9 -1.2 1.7 7.5 PhtD -1.2 -1.2 -4.0 -8.7	1.6 8.1 PiuA 4.4 2.8 1.2 -1.6 5.0 9 PiuA -1.1 -1.8 -1.8 -4.2	-1.1 1.4 Ply 1.0 1.7 -1.1 1.1 1.6 Ply -1.5 1.1 -1.7	-2.0 3.0 PsaA 4.7 1.2 -1.5 2.0 6.0 9 5.0 -1.3 -5.0 -9.1	-2.0 3.3 PspA 4.9 1.5 1.1 2.0 6.6 6.6 PspA -1.3 -4.3 -4.3 -5.9
F Allele A B C D E F Allele A B C D	-1.1 4.8 CbpA 2.7 1.4 -1.3 1.1 5.3 5.3 CbpA -2.0 -4.0 -6.8 -4.8	-2.3 3.9 GlpO 3.8 -1.3 -1.8 2.3 2.3 9.0 9.0 GlpO -2.4 -2.4 -11.8 -15.8 -3.9	1.0 3.8 MalX 4.0 -1.5 1.1 1.0 3.7 3.7 MalX 1.1 -5.6 -3.4 -3.8 2.7	-1.3 17.6 NanA 16.6 -1.2 -1.6 1.3 22.8 22.8 NanA -1.4 -27.8 -36.0 -17.6	-1.5 1.4 NanB 7.4 2.5 -1.1 1.5 2.1 2.1 NanB 3.5 1.2 -2.4 -1.4	-1.7 4.3 PhtD 6.3 1.9 -1.2 1.7 7.5 PhtD -1.2 -4.0 -8.7 -4.3	1.6 8.1 PiuA 4.4 2.8 1.2 -1.6 5.0 9iuA -1.1 -1.8 -4.2 -8.1	-1.1 1.4 Ply 1.0 1.7 -1.1 1.1 1.6 Ply -1.5 1.1 -1.7 -1.4	-2.0 3.0 PsaA 4.7 1.2 -1.5 2.0 6.0 6.0 PsaA -1.3 -5.0 -9.1 -3.0	-2.0 3.3 PspA 4.9 1.5 1.1 2.0 6.6 9 5.9 -1.3 -4.3 -5.9 -3.3 6.0
F Allele A B C D E F Allele A B C D E E	-1.1 4.8 CbpA 2.7 1.4 -1.3 1.1 5.3 5.3 CbpA -2.0 -4.0 -6.8 -4.8 -5.3	-2.3 3.9 GlpO 3.8 -1.3 -1.8 2.3 9.0 9.0 9.0 GlpO -2.4 -2.4 -11.8 -15.8 -3.9 -3.9	1.0 3.8 MalX 4.0 -1.5 1.1 1.0 3.7 3.7 MalX 1.1 -5.6 -3.4 -3.8 -3.7	-1.3 17.6 NanA 16.6 -1.2 -1.6 1.3 22.8 22.8 NanA -1.4 -27.8 -36.0 -17.6 -22.8	-1.5 1.4 NanB 7.4 2.5 -1.1 1.5 2.1 2.1 NanB 3.5 1.2 -2.4 -1.4 -2.1	-1.7 4.3 PhtD 6.3 1.9 -1.2 1.7 7.5 PhtD -1.2 -4.0 -8.7 -4.3 -4.3 -7.5	1.6 8.1 PiuA 4.4 2.8 1.2 -1.6 5.0 <b>PiuA</b> -1.1 -1.8 -4.2 -8.1 -5.0	-1.1 1.4 Ply 1.0 1.7 -1.1 1.1 1.6 Ply -1.5 1.1 -1.7 -1.4 -1.6	-2.0 3.0 PsaA 4.7 1.2 -1.5 2.0 6.0 6.0 PsaA -1.3 -5.0 -9.1 -3.0 -6.0	-2.0 3.3 PspA 4.9 1.5 1.1 2.0 6.6 9 6.6 -1.3 -4.3 -4.3 -5.9 -3.3 -5.9 -3.3

Allele    CbpA    GlpO    MaiX    NanA    NanB    PhtD    PiuA    Ply    PsaA    PspA      A	В	Protein Antigen Expression in TIGR4									
A    Image: Constraint of the second secon	Allele	CbpA	GlpO	MalX	NanA	NanB	PhtD	PiuA	Ply	PsaA	PspA
B    3.0    13.6    8.9    36.3    116.4    2.0    6.7    3.2    3.5    2.7      C    2.0    3.4    12.0    12.7    45.3    -1.9    -1.0    2.3    2.0    2.3      D    5.2    29.5    69.8    174.0    246.8    5.7    1.6    7.8    110.0    27.9      E    1.1    -6.1    -1.2    -2.8    32.3    -1.5    -2.8    1.8    -1.5    1.7      F    3.0    23.4    19.4    43.5    84.9    1.1    10.2    15.2    13.3    6.6      A    -3.0    13.6    -8.9    -36.3    -11.6    -1.7    -3.2    -3.5    -2.7      B    -    -    -1.3    -1.3    -2.8    -2.6    -3.2    -6.7    -1.4    -1.7    -1.2      D    1.7    2.2    7.8    4.8    2.1    3.3    -4.3    2.4    3.1    10.2	Α	-	-						-		-
C    2.0    3.4    12.0    12.7    45.3    -1.9    -1.0    2.3    2.0    2.3      D    5.2    29.5    69.8    174.0    246.8    5.7    1.6    7.8    11.0    27.9      E    1.1    -6.1    -1.2    2.8    323    -1.5    -2.8    1.8    -1.5    1.8    -1.5    1.8    -1.5    1.8    -1.5    1.8    -1.5    1.8    -1.5    1.8    -1.5    1.8    -1.5    1.7    F    3.0    13.6    -8.9    -6.0    -1.1    10.2    15.2    13.3    6.6      A    -3.0    13.6    -8.9    -6.0    -1.7    -6.7    -1.4    -1.7    -1.2    -1.7    1.2    -1.4    -1.5    1.5    4.1    1.0    1.0    1.7    2.2    1.2    -1.4    -1.5    1.8    -5.1    1.6      F    1.0    1.7    2.2    1.2    -1.4    -1.5    1.6 <td< td=""><td>В</td><td>3.0</td><td>13.6</td><td>8.9</td><td>36.3</td><td>116.4</td><td>2.0</td><td>6.7</td><td>3.2</td><td>3.5</td><td>2.7</td></td<>	В	3.0	13.6	8.9	36.3	116.4	2.0	6.7	3.2	3.5	2.7
D    5.2    29.5    69.8    174.0    246.8    5.7    1.6    7.8    11.0    27.9      E    1.1    -6.1    -1.2    -2.8    -32.3    -1.5    -2.8    1.8    -1.5    1.7      F    3.0    23.4    19.4    43.5    84.9    1.1    10.2    15.2    13.3    6.6      Allele    CbpA    GlpO    MalX    NanA    NanB    PhtD    PiuA    Ply    PsaA    PspA      A    -3.0    13.6    -8.9    -36.3    -116.4    -1.7    -6.7    -3.2    -3.5    -2.7      B    -    -    -    -    -    -    -    -    -    -    -    -    -1.4    -1.7    -1.2    -1.2    1.8    -1.4    -1.5    1.3    -1.8    -5.1    1.6    -1.8    -5.1    1.6    -1.8    -5.1    1.6    -1.8    -2.0    -2.3    -2.0    -2.3    -2.0 <td>С</td> <td>2.0</td> <td>3.4</td> <td>12.0</td> <td>12.7</td> <td>45.3</td> <td>-1.9</td> <td>-1.0</td> <td>2.3</td> <td>2.0</td> <td>2.3</td>	С	2.0	3.4	12.0	12.7	45.3	-1.9	-1.0	2.3	2.0	2.3
E    1.1    6.1    -1.2    -2.8    32.3    -1.5    -2.8    1.8    -1.5    1.7      F    3.0    23.4    19.4    43.5    84.9    1.1    10.2    15.2    13.3    6.6      Allele    CbpA    GlpO    MalX    NanA    NanB    PhtD    PiuA    Ply    PsaA    PspA      A    -3.0    -13.6    -8.9    -36.3    -116.4    -1.7    -6.7    -3.2    -3.5    -2.7      B	D	5.2	29.5	69.8	174.0	246.8	5.7	1.6	7.8	11.0	27.9
F    3.0    23.4    19.4    43.5    84.9    1.1    10.2    15.2    13.3    6.6      Allele    CbpA    GloD    MalX    NanA    NanB    PhD    PiuA    Ply    PsaA    PspA      A    -3.0    13.6    -8.9    -36.3    -11.64    -1.7    -6.7    -3.2    -3.5    -2.7      B	E	1.1	-6.1	-1.2	-2.8	-32.3	-1.5	-2.8	1.8	-1.5	1.7
Allee    CbpA    GlpO    MaiX    NanA    NanB    PhtD    PiuA    PiuA <t< td=""><td>F</td><td>3.0</td><td>23.4</td><td>19.4</td><td>43.5</td><td>84.9</td><td>1.1</td><td>10.2</td><td>15.2</td><td>13.3</td><td>6.6</td></t<>	F	3.0	23.4	19.4	43.5	84.9	1.1	10.2	15.2	13.3	6.6
Allele    CbpA    GlpO    MaX    NanA    NanB    PhtD    PiuA    Ply    PsaA    PspA      A    -3.0    -13.6    -8.9    -36.3    -116.4    -1.7    -6.7    -3.2    -3.5    -2.7      B    -    -    -    -    -    -    -    -    -											
A  -3.0  -13.6  -8.9  -36.3  -116.4  -1.7  -6.7  -3.2  -3.5  -2.7    B	Allele	CbpA	GlpO	MalX	NanA	NanB	PhtD	PiuA	Ply	PsaA	PspA
B    -	Α	-3.0	-13.6	-8.9	-36.3	-116.4	-1.7	-6.7	-3.2	-3.5	-2.7
C  -1.5  -4.0  1.3  -2.8  -2.6  -3.2  -6.7  -1.4  -1.7  -1.2    D  1.7  2.2  7.8  4.8  2.1  3.3  -4.3  2.4  3.1  10.2    E  -2.7  82.8  10.3  -102.5  3762.8  -2.6  18.9  -1.8  -5.1  -1.6    F  1.0  1.7  2.2  1.2  -1.4  -1.5  1.5  4.7  3.8  2.4    Allele  CbpA  GlpO  MalX  NanA  NanB  PhtD  PiuA  Ply  PsaA  PspA    A  -2.0  -3.4  -12.0  -12.7  45.3  3.5  1.0  -2.3  -2.0  -2.3    B  1.5  4.0  -1.3  2.8  2.6  7.1  6.7  1.4  1.7  1.2    C  -  -  -  -1.6  3.4  -2.3  -2.0  -2.3    D  2.6  8.7  5.8  13.6  5.5  19.7  1.6  3.4  5.4  12.3<	В										
D    1.7    2.2    7.8    4.8    2.1    3.3    -4.3    2.4    3.1    10.2      E    -2.7    -82.8    -10.3    -102.5    -3762.8    -2.6    -18.9    -1.8    -5.1    -1.6      F    1.0    1.7    2.2    1.2    -1.4    -1.5    1.5    4.7    3.8    2.4      A    -2.0    -3.4    -12.0    -1.2    -45.3    3.5    1.0    -2.3    -2.0    -2.3      B    1.5    4.0    -1.3    2.8    2.6    7.1    6.7    1.4    1.7    1.2      C    -    -    -    -    -    -    -    -    -    -    -    -    -    -    -    -2.3    -2.0    -2.3    2.0    -2.3    -2.0    -2.3    -2.0    -2.3    -2.0    -2.3    -2.0    -2.3    -2.3    -2.3    -2.3    -2.3    -2.3    -2.3    -2.3    -1.3 <td>С</td> <td>-1.5</td> <td>-4.0</td> <td>1.3</td> <td>-2.8</td> <td>-2.6</td> <td>-3.2</td> <td>-6.7</td> <td>-1.4</td> <td>-1.7</td> <td>-1.2</td>	С	-1.5	-4.0	1.3	-2.8	-2.6	-3.2	-6.7	-1.4	-1.7	-1.2
E    -2.7    82.8    -10.3    -102.5    -3762.8    -2.6    -18.9    -1.8    -5.1    -1.6      F    1.0    1.7    2.2    1.2    -1.4    -1.5    1.5    4.7    3.8    2.4      Allele    CbpA    GipO    Maix    NanA    NanB    PhtD    PiuA    Piy    PsaA    PspA      A    -2.0    -3.4    -12.0    -12.7    -45.3    3.5    1.0    -2.3    -2.0    -2.3      B    1.5    4.0    -1.3    2.8    2.6    7.1    6.7    1.4    1.7    1.2      C    -3.6    4.0    -1.3    2.8    2.6    7.1    6.7    1.4    1.7    1.2      C    -1.8    -20.8    13.8    -36.0    -146.3    2.3    -2.8    -1.3    -3.9    10.2    6.7    6.5    2.9      A    -5.2    -2.9    -6.98    -17.40    -246.8    -5.7    -1.6 <td>D</td> <td>1.7</td> <td>2.2</td> <td>7.8</td> <td>4.8</td> <td>2.1</td> <td>3.3</td> <td>-4.3</td> <td>2.4</td> <td>3.1</td> <td>10.2</td>	D	1.7	2.2	7.8	4.8	2.1	3.3	-4.3	2.4	3.1	10.2
F    1.0    1.7    2.2    1.2    -1.4    -1.5    1.5    4.7    3.8    2.4      Allele    CbpA    GlpO    MalX    NanA    NanB    PhtD    PiuA    Ply    PsaA    PspA      A    -2.0    -3.4    12.0    12.7    45.3    3.5    1.0    -2.3    2.0    -2.3      B    1.5    4.0    -1.3    2.8    2.6    7.1    6.7    1.4    1.7    1.2      C    -    -    -    -    -    -    -    -    -      D    2.6    8.7    5.8    13.6    5.5    19.7    1.6    3.4    5.4    1.3      F    1.5    6.9    1.6    3.4    1.9    3.9    10.2    6.7    6.5    2.9      A    -5.2    -295    -698    174.0    -246.8    -5.7    7.16    -7.8    -11.0    -27.9      B    -1.7	E	-2.7	-82.8	-10.3	-102.5	-3762.8	-2.6	-18.9	-1.8	-5.1	-1.6
Allele    CbpA    GlpO    MalX    NanA    NanB    PhtD    PiuA    Ply    PsaA    PspA      A    -2.0    -3.4    -12.0    -12.7    -45.3    3.5    1.0    -2.3    -2.0    -2.3      B    1.5    4.0    -1.3    2.8    2.6    7.1    6.7    1.4    1.7    1.2      C    - <td< td=""><td>F</td><td>1.0</td><td>1.7</td><td>2.2</td><td>1.2</td><td>-1.4</td><td>-1.5</td><td>1.5</td><td>4.7</td><td>3.8</td><td>2.4</td></td<>	F	1.0	1.7	2.2	1.2	-1.4	-1.5	1.5	4.7	3.8	2.4
Allele    CbpA    GipO    MalX    NanA    NanB    PhtD    PiuA    Ply    PsaA    PspA      A    -2.0    -3.4    -12.0    -12.7    -45.3    3.5    1.0    -2.3    -2.0    -2.3      B    1.5    4.0    -1.3    2.8    2.6    7.1    6.7    1.4    1.7    1.2      C    - <td< th=""><th></th><th></th><th></th><th></th><th></th><th></th><th></th><th></th><th></th><th></th><th></th></td<>											
A  -2.0  -3.4  -12.0  -12.7  -45.3  3.5  1.0  -2.3  -2.0  -2.3    B  1.5  4.0  -1.3  2.8  2.6  7.1  6.7  1.4  1.7  1.2    C	Allele	CbpA	GlpO	MalX	NanA	NanB	PhtD	PiuA	Ply	PsaA	PspA
B    1.5    4.0    -1.3    2.8    2.6    7.1    6.7    1.4    1.7    1.2      C    I	A	-2.0	-3.4	-12.0	-12.7	-45.3	3.5	1.0	-2.3	-2.0	-2.3
C    Image: Marking the second state of the secon	В	1.5	4.0	-1.3	2.8	2.6	7.1	6.7	1.4	1.7	1.2
D  2.6  8.7  5.8  13.6  5.5  19.7  1.6  3.4  5.4  12.3    E  -1.8  -20.8  -13.8  -36.0  -1463.5  2.3  -2.8  -1.3  -2.9  -1.3    F  1.5  6.9  1.6  3.4  1.9  3.9  10.2  6.7  6.5  2.9    A  -5.2  -29.5  69.8  -174.0  -246.8  -5.7  -1.6  -7.8  -11.0  -27.9    B  -1.7  -2.2  -7.8  -4.8  -2.1  -2.8  4.3  -2.4  -3.1  -10.2    C  -2.6  -8.7  -5.8  -13.6  -5.5  -10.6  -1.6  -3.4  -5.4  -12.3    D  - <td>С</td> <td></td>	С										
E  -1.8  -20.8  -13.8  -36.0  -1463.5  2.3  -2.8  -1.3  -2.9  -1.3    F  1.5  6.9  1.6  3.4  1.9  3.9  10.2  6.7  6.5  2.9    Allele  CbpA  GlpO  MalX  NanA  NanB  PhtD  PiuA  Ply  PsaA  PspA    A  -5.2  -29.5  -69.8  -174.0  -246.8  -5.7  -1.6  -7.8  -11.0  -27.9    B  -1.7  -2.2  -7.8  -4.8  -2.1  -2.8  4.3  -2.4  -3.1  -10.2    C  -2.6  -8.7  -5.8  -13.6  -5.5  -10.6  -1.6  -3.4  -5.4  -12.3    D  -	D	2.6	8.7	5.8	13.6	5.5	19.7	1.6	3.4	5.4	12.3
F  1.5  6.9  1.6  3.4  1.9  3.9  10.2  6.7  6.5  2.9    Allele  CbpA  GlpO  MalX  NanA  NanB  PhtD  PiuA  Ply  PsaA  PspA    A  -5.2  -29.5  -69.8  -174.0  -246.8  -5.7  -1.6  -7.8  -11.0  -27.9    B  -1.7  -2.2  -7.8  -4.8  -2.1  -2.8  4.3  -2.4  -3.1  -10.2    C  -2.6  -8.7  -5.8  -13.6  -5.5  -10.6  -1.6  -3.4  -5.4  -12.3    D	E	-1.8	-20.8	-13.8	-36.0	-1463.5	2.3	-2.8	-1.3	-2.9	-1.3
Allele    CbpA    GlpO    MalX    NanA    NanB    PhtD    PiuA    Ply    PsaA    PspA      A    -5.2    -29.5    -69.8    -174.0    -246.8    -5.7    -1.6    -7.8    -11.0    -27.9      B    -1.7    -2.2    -7.8    -4.8    -2.1    -2.8    4.3    -2.4    -3.1    -10.2      C    -2.6    -8.7    -5.8    -13.6    -5.5    -10.6    -1.6    -3.4    -5.4    -12.3      D    -	F	1.5	6.9	1.6	3.4	1.9	3.9	10.2	6.7	6.5	2.9
Allele    CbpA    GlpO    MalX    NanA    NanB    PhtD    PiuA    Ply    PsaA    PspA      A    -5.2    -29.5    -69.8    -174.0    -246.8    -5.7    -1.6    -7.8    -11.0    -27.9      B    -1.7    -2.2    -7.8    -4.8    -2.1    -2.8    4.3    -2.4    -3.1    -10.2      C    -2.6    -8.7    -5.8    -13.6    -5.5    -10.6    -1.6    -3.4    -5.4    -12.3      D    -											
A  -5.2  -29.5  -69.8  -174.0  -246.8  -5.7  -1.6  -7.8  -11.0  -27.9    B  -1.7  -2.2  -7.8  -4.8  -2.1  -2.8  4.3  -2.4  -3.1  -10.2    C  -2.6  -8.7  -5.8  -13.6  -5.5  -10.6  -1.6  -3.4  -5.4  -12.3    D  - <td>Allele</td> <td>CbpA</td> <td>GlpO</td> <td>MalX</td> <td>NanA</td> <td>NanB</td> <td>PhtD</td> <td>PiuA</td> <td>Ply</td> <td>PsaA</td> <td>PspA</td>	Allele	CbpA	GlpO	MalX	NanA	NanB	PhtD	PiuA	Ply	PsaA	PspA
B  -1.7  -2.2  -7.8  -4.8  -2.1  -2.8  4.3  -2.4  -3.1  -10.2    C  -2.6  -8.7  -5.8  -13.6  -5.5  -10.6  -1.6  -3.4  -5.4  12.3    D	A	-5.2	-29.5	-69.8	-174.0	-246.8	-5.7	-1.6	-7.8	-11.0	-27.9
C  -2.6  -8.7  -5.8  -13.6  -5.5  -10.6  -1.6  -3.4  -5.4  -12.3    D  -	В	-1.7	-2.2	-7.8	-4.8	-2.1	-2.8	4.3	-2.4	-3.1	-10.2
D    -4.7    -179.7    -80.6    -491.0    -7981.1    -8.5    -4.4    -4.4    -16.0    -16.0      F    -1.7    -1.3    -3.6    -4.0    -2.9    -5.0    6.5    2.0    1.2    -4.2      Allele    CbpA    GlpO    MaiX    NanA    NanB    PhtD    PiuA    Ply    PsaA    PspA      A    -1.1    6.1    1.2    2.8    32.3    1.5    2.8    -1.8    1.5    -1.7      B    2.7    82.8    10.3    102.5    3762.8    3.1    18.9    1.8    5.1    1.6      C    1.8    20.8    13.8    36.0    1463.5    -1.3    2.8    1.3    2.9    1.3      D    4.7    179.7    80.6    491.0    7981.1    8.5    4.4    4.4    16.0    16.0      E    -    -    -    -    -    -    -    -      F    2.7	C	-2.6	-8.7	-5.8	-13.6	-5.5	-10.6	-1.6	-3.4	-5.4	-12.3
E  -4.7  -179.7  -80.6  -491.0  -7981.1  -8.5  -4.4  -4.4  -16.0  -16.0    F  -1.7  -1.3  -3.6  -4.0  -2.9  -5.0  6.5  2.0  1.2  -4.2    Allele  CbpA  GlpO  MalX  NanA  NanB  PhtD  PiuA  Ply  PsaA  PspA    A  -1.1  6.1  1.2  2.8  32.3  1.5  2.8  -1.8  1.5  -1.7    B  2.7  82.8  10.3  102.5  3762.8  3.1  18.9  1.8  5.1  1.6    C  1.8  20.8  13.8  36.0  1463.5  -1.3  2.8  1.3  2.9  1.3    D  4.7  179.7  80.6  491.0  7981.1  8.5  4.4  4.4  16.0  16.0    E	D										
F  -1.7  -1.3  -3.6  -4.0  -2.9  -5.0  6.5  2.0  1.2  -4.2    Allele  CbpA  GlpO  MalX  NanA  NanB  PhtD  PiuA  Ply  PsaA  PspA    A  -1.1  6.1  1.2  2.8  32.3  1.5  2.8  -1.8  1.5  -1.7    B  2.7  82.8  10.3  102.5  3762.8  3.1  18.9  1.8  5.1  1.6    C  1.8  20.8  13.8  36.0  1463.5  -1.3  2.8  1.3  2.9  1.3    D  4.7  179.7  80.6  491.0  7981.1  8.5  4.4  4.4  16.0  16.0    E	E	-4.7	-179.7	-80.6	-491.0	-7981.1	-8.5	-4.4	-4.4	-16.0	-16.0
AlleleCbpAGlpOMalXNanANanBPhtDPiuAPlyPsaAPspAA-1.16.11.22.832.31.52.8-1.81.5-1.7B2.782.810.3102.53762.83.118.91.85.11.6C1.820.813.836.01463.5-1.32.81.32.91.3D4.7179.780.6491.07981.18.54.44.416.016.0EF2.7143.022.4122.92747.01.728.78.619.33.8AlleleCbpAGlpOMalXNanANanBPhtDPiuAPlyPsaAPspAA-3.0-23.4-19.4-43.5-84.9-1.1-10.2-15.2-13.3-6.6B-1.0-1.7-2.2-1.21.41.8-1.5-4.7-3.8-2.4	F	-1.7	-1.3	-3.6	-4.0	-2.9	-5.0	6.5	2.0	1.2	-4.2
Allele    CbpA    GlpO    MalX    NanA    NanB    PhtD    PiuA    Ply    PsaA    PspA      A    -1.1    6.1    1.2    2.8    32.3    1.5    2.8    -1.8    1.5    -1.7      B    2.7    82.8    10.3    102.5    3762.8    3.1    18.9    1.8    5.1    1.6      C    1.8    20.8    13.8    36.0    1463.5    -1.3    2.8    1.3    2.9    1.3      D    4.7    179.7    80.6    491.0    7981.1    8.5    4.4    4.4    16.0    16.0      E    - <td< th=""><th></th><th></th><th></th><th></th><th></th><th></th><th></th><th></th><th></th><th></th><th></th></td<>											
A  -1.1  6.1  1.2  2.8  32.3  1.5  2.8  -1.8  1.5  -1.7    B  2.7  82.8  10.3  102.5  3762.8  3.1  18.9  1.8  5.1  1.6    C  1.8  20.8  13.8  36.0  1463.5  -1.3  2.8  1.3  2.9  1.3    D  4.7  179.7  80.6  491.0  7981.1  8.5  4.4  4.4  16.0  16.0    E	Allele	CbpA	GlpO	MalX	NanA	NanB	PhtD	PiuA	Ply	PsaA	PspA
B  2.7  82.8  10.3  102.5  3762.8  3.1  18.9  1.8  5.1  1.6    C  1.8  20.8  13.8  36.0  1463.5  -1.3  2.8  1.3  2.9  1.3    D  4.7  179.7  80.6  491.0  7981.1  8.5  4.4  4.4  16.0  16.0    E	A	-1.1	6.1	1.2	2.8	32.3	1.5	2.8	-1.8	1.5	-1.7
C  1.8  20.8  13.8  36.0  1463.5  -1.3  2.8  1.3  2.9  1.3    D  4.7  179.7  80.6  491.0  7981.1  8.5  4.4  4.4  16.0  16.0    E	В	2.7	82.8	10.3	102.5	3762.8	3.1	18.9	1.8	5.1	1.6
D  4.7  179.7  80.6  491.0  7981.1  8.5  4.4  4.4  16.0  16.0    E  Image: Constraint of the state of	C	1.8	20.8	13.8	36.0	1463.5	-1.3	2.8	1.3	2.9	1.3
E  Image: Constraint of the stress of the	D	4.7	179.7	80.6	491.0	7981.1	8.5	4.4	4.4	16.0	16.0
F  2.7  143.0  22.4  122.9  2747.0  1.7  28.7  8.6  19.3  3.8    Allele  CbpA  GlpO  MalX  NanA  NanB  PhtD  PiuA  Ply  PsaA  PspA    A  -3.0  -23.4  -19.4  -43.5  -84.9  -1.1  -10.2  -15.2  -13.3  -6.6    B  -1.0  -1.7  -2.2  -1.2  1.4  1.8  -1.5  -4.7  -3.8  -2.4	E										
Allele    CbpA    GlpO    MalX    NanA    NanB    PhtD    PiuA    Ply    PsaA    PspA      A    -3.0    -23.4    -19.4    -43.5    -84.9    -1.1    -10.2    -15.2    -13.3    -6.6      B    -1.0    -1.7    -2.2    -1.2    1.4    1.8    -1.5    -4.7    -3.8    -2.4	F	2.7	143.0	22.4	122.9	2747.0	1.7	28.7	8.6	19.3	3.8
Allele    CbpA    GIpO    Maix    NanA    NanB    PhtD    PiuA    Ply    PsaA    PspA      A    -3.0    -23.4    -19.4    -43.5    -84.9    -1.1    -10.2    -15.2    -13.3    -6.6      B    -1.0    -1.7    -2.2    -1.2    1.4    1.8    -1.5    -4.7    -3.8    -2.4					<b>NI A</b>			<b>D</b> : 4	<b>D</b> .	<b>.</b>	<b>.</b>
A    -3.0    -23.4    -19.4    -43.5    -84.9    -1.1    -10.2    -15.2    -13.3    -6.6      B    -1.0    -1.7    -2.2    -1.2    1.4    1.8    -1.5    -4.7    -3.8    -2.4	Allele	СррА	GipO	Walx	NanA	NanB	PhtD	PiuA	Ply	PsaA	PSpA
В -1.0 -1.7 -2.2 -1.2 1.4 1.8 -1.5 -4.7 -3.8 -2.4	A	-3.0	-23.4	-19.4	-43.5	-84.9	-1.1	-10.2	-15.2	-13.3	-6.6
	В	-1.0	-1./	-2.2	-1.2	1.4	1.8	-1.5	-4.7	-3.8	-2.4
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		-1.5	-6.9	-1.6	-3.4	-1.9	-2.1	-10.2	-6.7	-0.5	-2.9
D    1.1    1.3    3.6    4.0    2.9    5.0    -b.5    -2.0    -1.2    4.2      E    2.7    142.0    22.4    122.0    27.7    1.7    20.7    1.0    2.0    2.0    2.0		2.7	1.3	3.0	4.0	2.9	5.0	-6.5	-2.0	-1.2	4.2
E -2.7 -143.0 -22.4 -122.9 -2147.0 -1.7 -20.7 -0.0 -19.3 -3.8		-2.1	-143.0	-22.4	-122.9	-2141.0	-1./	-26.7	-0.0	-19.3	-3.8

Supplementary Table 2. Putative vaccine target RTqPCR. Heatmap of putative vaccine target gene expression across strains A) D39 and B) TIGR4 expressing individual SpnDIII alleles ranging from red

(- fold difference) to green (+ fold difference). Gene expression values from locked alleles in grey have been used as a baseline against other alleles.

Primer Name	Forward/Reverse	Sequence (5' - 3')
CbpA_RT_F	F	CAAGGTAAACCAAAGGGGCG
CbpA_RT_R	R	TCAGGGATGAGCTTGGAAGAG
GlpO_RT_F	F	CATTGCCAACCACGTGAAGG
GlpO_RT_R	R	AACCAGACGGGCCTTGATTT
MalX_RT_F	F	TACGCATTCGCTGGTGAAGA
MalX_RT_R	R	AGCGTCTTTACCGTTTTGGC
NanA_RT_F	F	ATGACGACGGGAAGACATGG
NanA_RT_R	R	TTGTGAGGCCCATTCCGAAG
NanB_RT_F	F	TCTAGAAGTGGCCGTAAGGGA
NanB_RT_R	R	AGGCATAACCATACGAAGGCAA
PhtD_RT_F	F	AGCTGTTCGAAAAGTAGGCGA
PhtD_RT_R	R	ACTTTCCTGCTTGGCCAGTT
Ply_RT_F	F	CCCACTCTTCTTGCGGTTGA
Ply_RT_R	R	TCCGCGAACACTTGAATTGC
PspA_RT_R	F	CGCTCCTCAAGCTAAAATCGC
PspA_RT_R	R	GAAGAGGAGCACGGAAACCT
PiuA_RT_F	F	CCGAAGGCACTTGCTAAGGA
PiuA_RT_R	R	TCGCTTCACCACGTACACAA
PsaA_RT_F	F	CAGCGACGGCGTTGATGTTA
PsaA_RT_R	R	TTGGCGCTCAATTGTTTGGC
lytA_RT_F	F	CGGTTGGAATGCTGAGACCT
lytA_RT_R	R	GGCAAACCTGCTTCATCTGC
T4_PspA_RT_F	F	CCAGCGTCGCTATCTTAGGG
T4_PspA_RT_R	R	TCTTGGCAGTATCAGCTTTTGC
T4_PhtD_RT_F	F	AGCAGTAGTTGCAGCCAGAG
T4_PhtD_RT_R	R	TAATGGTCGCCGTGAGGAAC
16s_RT_F	F	AACCAAGTAACTTTGAAAGAAGAC
16s_RT_R	R	AAATTTAGAATCGTGGAATTTTT

Supplementary Table 3. RTqPCR Primers.

## Supplementary Figure 1



**Supplementary Figure 1**. Balanced *S. pneumoniae* D39 SpnIII locked allele inputs. Input colony forming unit (CFU) loads were standardised for experiments. A multiplicity of infection (MOI) of ~100:1 (CFU:A549) was used for adherence and invasion to A549 cells (A) and ~5:1 (CFU:Airway Cell) for adherence to human airway cells (B). 1000 CFU per well were used in neutrophil killing and opsonophagocytic killing assays (C). Approximately 50 000 CFU per well were used in the whole blood killing assay (D).

## **Supplementary Figure 2**







GlpO















**Supplementary Figure 2A.** Full images of vaccine candidate Western Blots. Full scans of Western Blots using vaccine candidate anti-sera against *S. pneumoniae* D39 and TIRG4 locked SpnIII alleles. The outlined section of each Blot has been used in **Figure 3**.



**Supplementary Figure 2B.** Balanced loading of locked allele lysates for Western Blots. D39 and TIGR4 locked allele cell lysate loads were standardised via Coomassie stain to ensure equal protein loading was used in vaccine candidate Western Blots used in **Figure 3** and **Supplementary Figure 2A**.



**Quantitative Western Blot** 



## Fold Difference from Most Intense Band

PiuA Fold	Difference	PsaA Fold Difference				
B vs A	2.7	D vs A	1.1			
B vs C	2.3	D vs B	1.1			
B vs D	2.4	D vs C	1.2			
B vs E	1.2	D vs E	1.5			
B vs E	1.7	D vs F	1.2			

**Supplementary Figure 2C.** PiuA and PsaA ELISA with comparative Western Blot and quantified Western Blot values. Western Blot banding intensity was quantified in ImageJ. Fold differences calculated from the quantified Western Blot values are provided, using the most intense band as a baseline for comparison.