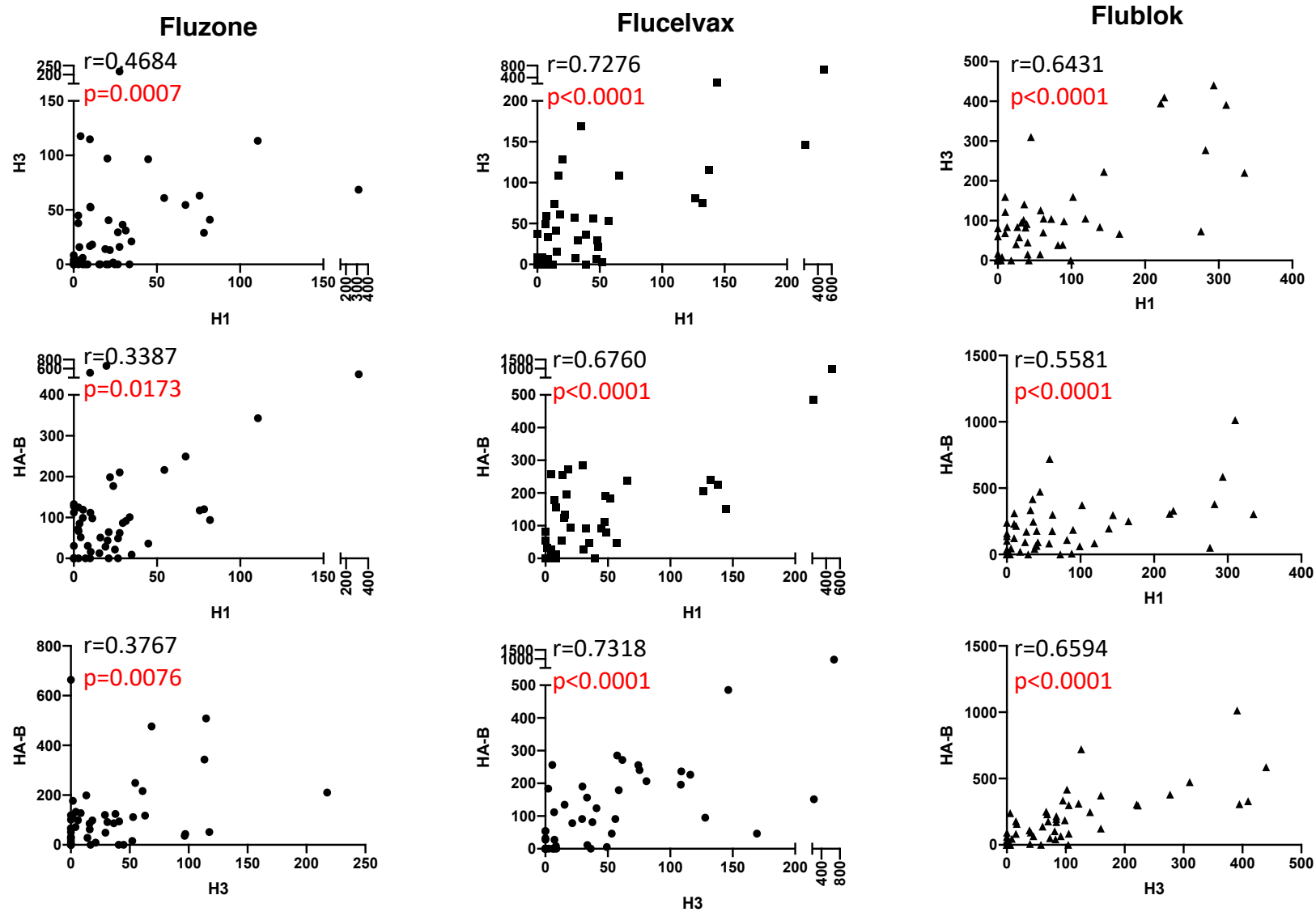
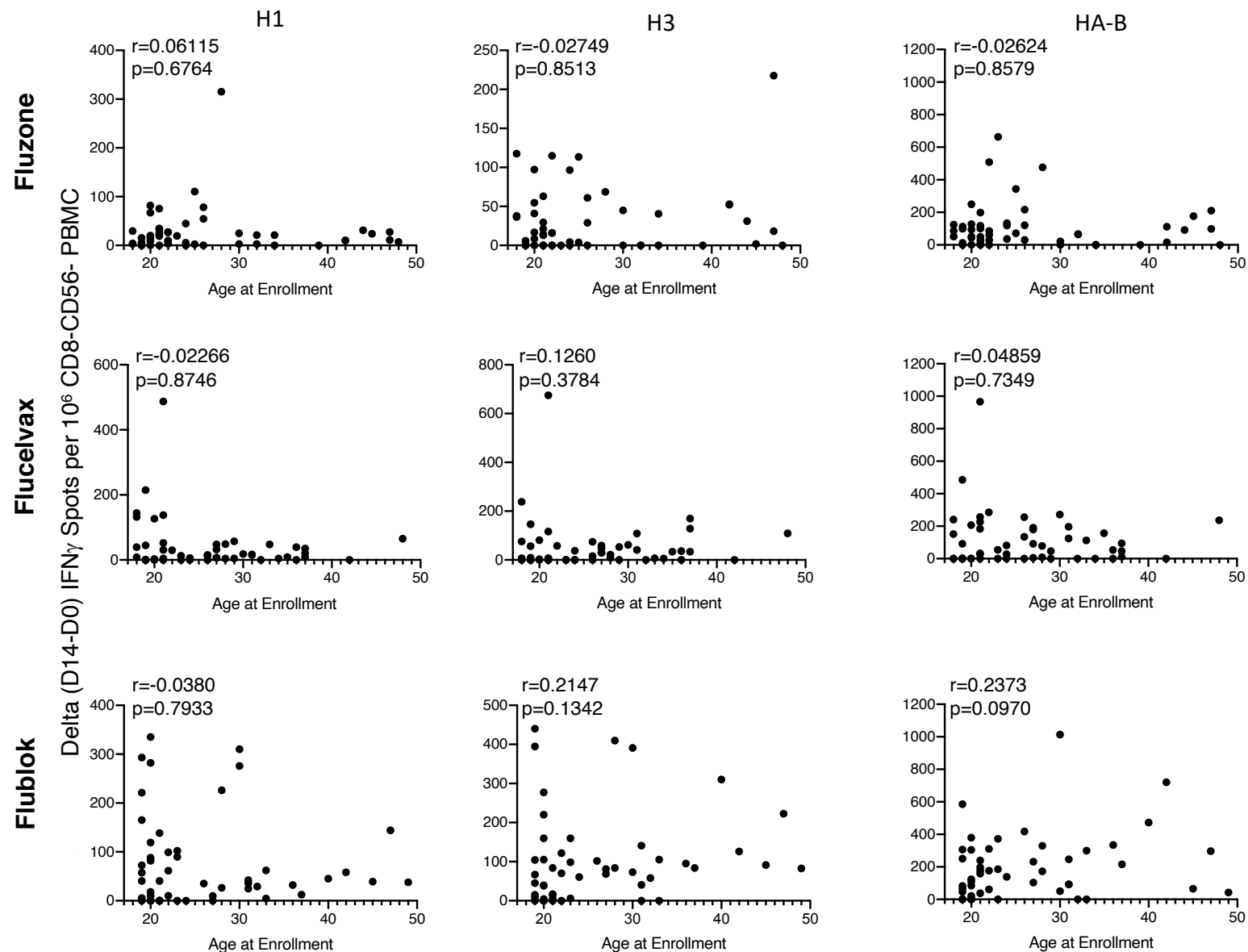


2015 (Yr1)	Fluzone (15µg ea HA)	Flucelvax (15µg ea HA)	Flublok (45µg ea HA)
H1N1	A/California/07/2009	A/Brisbane/10/2010	A/California/07/2009
H3N2	A/Switzerland/9715293/2013	A/South Australia/55/2014	A/Switzerland/9715293/2013
B/Victoria	B/Brisbane/60/2008		
B/Yamagata	B/Phuket/3073/2013	B/Utah/9/2014	B/Phuket/3073/2013
2016 (Yr2)	Fluzone (15µg ea HA)	Flucelvax (15µg ea HA)	Flublok (45µg ea HA)
H1N1	A/California/07/2009	A/Brisbane/10/2010	A/California/07/2009
H3N2	A/Hong Kong/4801/2014	A/Hong Kong/4801/2014	A/Hong Kong/4801/2014
B/Victoria	B/Brisbane/60/2008	B/Hong Kong/259/2010	B/Brisbane/60/2008
B/Yamagata	B/Phuket/3073/2013	B/Utah/9/2014	
2017 (Yr3)	Fluzone (15µg ea HA)	Flucelvax (15µg ea HA)	Flublok (45µg ea HA)
H1N1	A/Michigan/45/2015 X-275	A/Singapore/GP1908/2015 IVR-180	A/Michigan/45/2015
H3N2	A/Hong Kong/4801/2014 X-263B	A/Singapore/GP2050/2015	A/Hong Kong/4801/2014
B/Victoria	B/Brisbane/60/2008	B/Hong Kong/259/2010	B/Brisbane/60/2008
B/Yamagata	B/Phuket/3073/2013	B/Utah/9/2014	B/Phuket/2073/2013

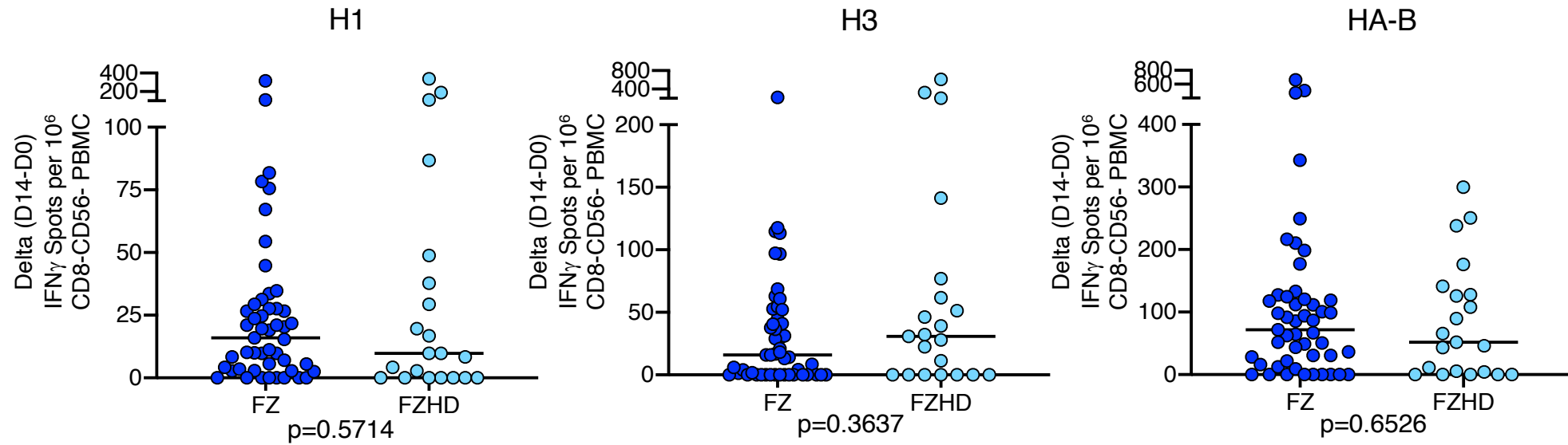
Supplementary Figure 1. Vaccine Composition. The viral strains included in each of the licensed vaccines used in this study.



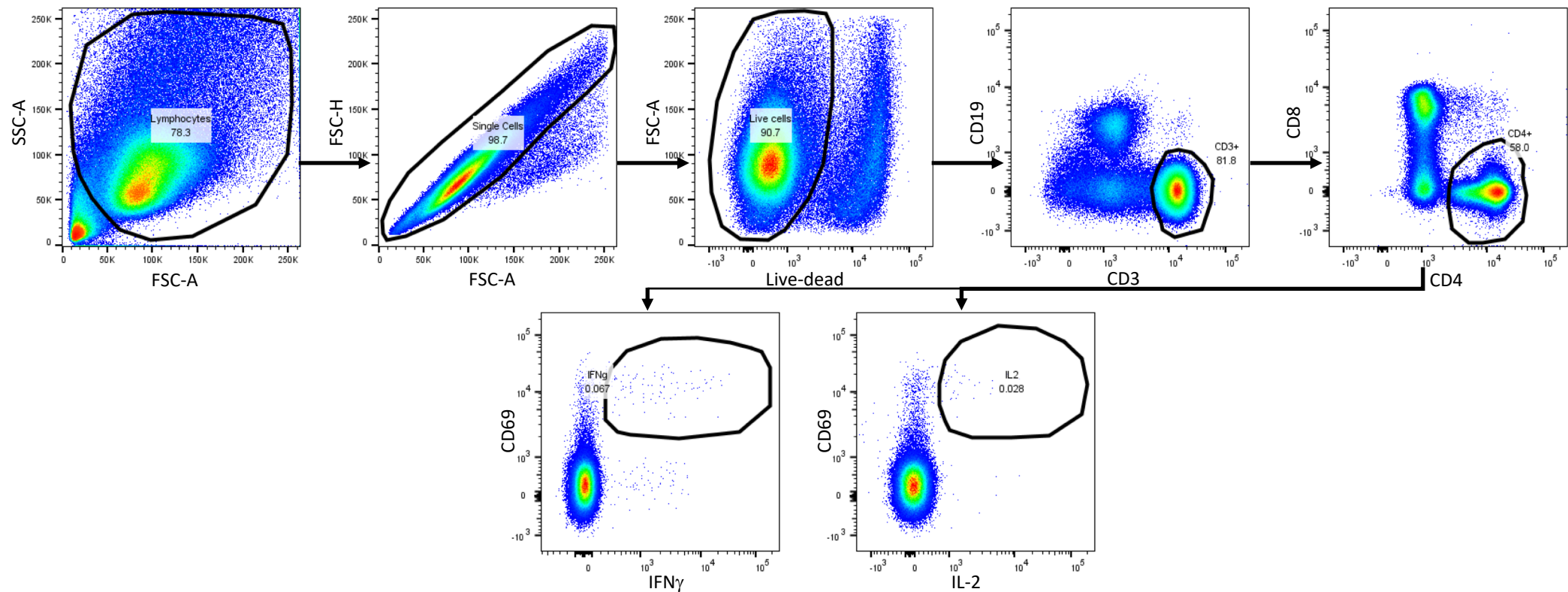
Supplementary Figure 2. Relationships between HA specific CD4 T cell responses post vaccination. Human subjects were vaccinated with one of the three licensed influenza vaccines Fluzone (left), Flucelvax (middle) or Flublok (right). CD4-enriched populations were stimulated with pools of peptides from the HA indicated on each axis. IFN γ cytokine producing cells were quantified using EliSpot assays. The data is presents as the change between day 14 and day 0 (D14-D0) of the number of IFN γ producing cells per million CD8-CD56- PBMC. The correlation between the CD4 responses for H1 and H3 (top row), H1 and HA-B (middle row) and H3 and HA-B (bottom row) are shown. The r and p values are indicated in the top left corner of each panel and were calculated using the non-parametric Spearman correlation.



Supplementary Figure 3. The pattern of CD4 T cell responses post vaccination based on age. Human subjects were vaccinated with one of the three licensed influenza vaccines, Fluzone (top), Flucelvax (middle) or Flublok (bottom). CD4-enriched populations were stimulated with the pools of peptides from each HA protein indicated above each column. IFN- γ cytokine-producing cells were quantified using EliSpot assays. The data is presented as the change in response between day 14 and day 0 (D14-D0) of the number of IFN- γ producing cells per million CD8-CD56- PBMC, indicated on the y-axis and age is indicated on the x-axis. The r and p values are indicated in the top left corner of each panel and were calculated using the non-parametric Spearman correlation.



Supplementary Figure 4. CD4 T cell response post vaccination is not determined by HA dose within the vaccine. A group of 21 healthy subjects, aged 18-49 years old were vaccinated with high dose trivalent Fluzone (light blue) and compared to subjects that received quadrivalent Fluzone (dark blue). CD4-enriched populations from each group were stimulated with pools of peptides from H1, H3 and HA-B and evaluated for IFN-γ production using cytokine ELISpot assays. The data are represented as the change in the response between day 0 and day 14 (D14-D0) with the median response indicated by a black line. The specific HA reactivity is indicated above the panels, with H1 on the left, H3 in the middle and HA-B on the right. The p values shown were calculated by the Wilcoxon rank sum test.



Supplementary Figure 5: Representative plot of the sequential gating strategy utilized to identify activated cells that express IFN γ and/or IL-2. PBMCs isolated from vaccinated subjects were stimulated in vitro with peptide pools of interest, with brefeldin A and monensin added for the last 8 hours of culture to block cytokine secretion. Surface and intracellular cytokine staining were performed and data acquired on a BD LSR-II flow cytometer. After exclusion of debris and doublets, cells were gated on live, CD3+, CD4+ T cells that expressed CD69 together with IFN γ and/or IL-2.

Fluzone				Flucelvax				Flublok			
Subject No.	Gender	Previous Vaccination	Age	Subject No.	Gender	Previous Vaccination	Age	Subject No.	Gender	Previous Vaccination	Age
1	M	N	25	10	M	N	30	22	F	Y	21
2	F	Y	48	11	F	N	19	23	F	N	47
3	M	N	18	12	F	Y	29	24	F	Y	20
4	F	U	18	13	M	N	31	25	M	N	19
5	M	N	34	14	M	Y	29	26	F	Y	37
6	F	Y	47	15	F	Y	37	27	M	N	30
7	F	Y	45	16	M	Y	26	28	M	N	19
8	M	Y	23	17	F	Y	19	29	M	N	28
9	M	Y	18	18	M	Y	42	30	F	N	20
33	F	Y	44	19	F	Y	34	31	M	Y	20
34	M	Y	20	20	F	N	36	32	F	Y	19
35	M	Y	22	21	M	Y	19	69	M	Y	49
36	M	Y	25	51		U	32	70	F	U	26
37	M	Y	32	52	F	N	48	71	F	Y	33
38	F	Y	47	53	F	N	18	72	F	Y	32
39	F	U	19	54	M	Y	27	73	M	Y	33
40	M	Y	21	55	F	N	22	74	F	Y	19
41	M	Y	26	56	F	Y	24	75	F	N	24
42	M	Y	30	57	F	Y	21	76	F	N	22
43	M	Y	26	58	F	Y	35	77	F	Y	42
44	M	N	20	59	F	N	21	78	F	Y	45
45	F	Y	21	60	F	N	26	79	F	Y	23
46	F	Y	42	61	F	N	31	80	M	Y	20
47	F	U	21	62	F	Y	24	81	F	Y	19
48	M	Y	19	63	F	Y	34	82	F	Y	31
49	F	Y	20	64	F	N	21	83	F	N	19
50	F	N	26	65	F	Y	24	84	F	N	20
88	M	Y	32	66	M	Y	37	85	F	N	40
89	F	N	30	67	M	N	20	86	F	Y	30
90	M	N	22	68	M	N	19	87	M	Y	22
91	M	N	24	111	F	Y	37	133	F	N	31
92	M	Y	20	112	F	Y	33	134	M	Y	31
93	M	Y	20	113	F	Y	19	135	M	Y	20
95	M	N	24	114	F	N	21	136	M	Y	20
96	F	N	22	115	M	N	21	137	F	N	21
97	M	Y	21	116	M	Y	26	138	F	N	27
98	F	N	42	117	M	N	28	139	F	Y	19
99	F	N	21	118	F	Y	19	140	F	Y	28
100	M	Y	22	119	M	Y	23	141	F	N	19
101	M	Y	19	120	F	N	27	142	F	N	27
102	M	Y	19	121	M	Y	23	143	F	Y	23
103	F	Y	34	122	M	Y	18	144	F	Y	21
104	M	Y	39	123	F	Y	20	145	F	Y	23
105	F	Y	21	124	F	Y	28	146	F	N	20

106	F	Y	24	125	M	N	20	147	F	Y	21
107	M	Y	20	126	F	Y	18	148	M	Y	22
108	M	U	28	127	M	Y	18	149	M	N	21
109	F	U	21	128	M	Y	36	150	F	Y	20
110	M	N	22	129	M	Y	21	151	F	N	20
				130	M	N	27	152	F	Y	36
				131	M	Y	27				
				132	F	N	21				

Supplemental Table 1. Vaccine comparison study subject demographics. The subject numbers, age, gender and self-reported vaccination status from the previous season are indicated. Vaccination status for the influenza season prior to enrollment was reported as received a vaccine (Y), did not receive vaccine (N), or were unsure (U) if vaccinated last season.