Supplemental Table 1. Crude antibody responses pre-vaccination and at one month post-vaccination by hemagglutination inhibition against cell-grown vaccine reference viruses† among recipients of high-dose egg-based, standard-dose egg-based, cell culture-based and recombinant influenza vaccines, per protocol population‡, N=390

	SD-IIV4 (n=102)			**HD-IIV3 (n=79)**			**ccIIV4 (n=106)**			**RIV4 (n=103)**		
	Day 0[a]	One Month[a]	P-value[b]	Day 0[a]	One Month[a]	P-value[b]	Day 0[a]	One Month[a]	P-value[b]	Day 0[a]	One Month[a]	P-value[b]
A/H1N1												
Seroconversion Rate (SCR)	–	7% (3-18%)	REF	–	10% (4-25%)	0.432	–	26% (17-41%)	**<0.001**	–	27% (18-42%)	**<0.001**
Geometric Mean Titer (GMT)	29.3 (20.5-41.7)	42.2 (29.7-60.0)	REF	23.2 (15.5-34.7)	36.0 (24.2-53.7)	0.416	26.2 (18.5-37.0)	56.9 (40.3-80.4)	0.101	28.6 (20.1-40.6)	69.0 (48.6-97.9)	0.008
Mean-fold Rise in GMT	–	1.4 (1.2-1.7)	REF	–	1.6 (1.2-1.9)	0.501	–	2.2 (1.8-2.6)	**<0.001**	–	2.4 (2.0-2.9)	**<0.001**
HI titer ≥1:40	–	67% (55-81%)	REF	–	58% (45-75%)	0.252	–	71% (60-84%)	0.526	–	73% (62-86%)	0.339
HI titer ≥1:80	–	44% (33-60%)	REF	–	41% (28-59%)	0.628	–	54% (42-69%)	0.167	–	58% (47-73%)	0.046
HI titer ≥1:160	–	24% (15-38%)	REF	–	22% (12-38%)	0.749	–	34% (24-49%)	0.101	–	38% (27-53%)	0.030
A/H3N2												
Seroconversion Rate (SCR)	–	28% (19-43%)	REF	–	44% (32-62%)	0.028	–	28% (19-43%)	0.984	–	46% (34-61%)	0.013
Geometric Mean Titer (GMT)	58.9 (43.6-79.6)	121.9 (90.3-164.6)	REF	26.3 (18.6-37.0)	64.8 (46.1-91.1)	**<0.001**	49.0 (36.5-65.8)	103.2 (76.9-138.6)	0.284	56.4 (41.8-76.1)	178.2 (132.2-240.2)	0.016
Mean-fold Rise in GMT	–	2.1 (1.6-2.7)	REF	–	2.5 (1.8-3.4)	0.247	–	2.1 (1.6-2.8)	0.897	–	3.2 (2.4-4.1)	**0.003**
HI titer ≥1:40	–	90% (83-99%)	REF	–	85% (75-96%)	0.286	–	90% (82-98%)	0.891	–	96% (91-100%)	0.096
HI titer ≥1:80	–	77% (67-89%)	REF	–	53% (40-71%)	**0.002**	–	70% (59-83%)	0.212	–	89% (751-100%)	0.024
HI titer ≥1:160	–	57% (45-72%)	REF	–	24% (14-41%)	**<0.001**	–	54% (42-69%)	0.654	–	74% (63-86%)	0.013
B/Victoria												
Seroconversion Rate (SCR)	–	6% (2-17%)	REF	–	8% (3-22%)	0.647	–	8% (4-20%)	0.470	–	23% (14-38%)	**0.002**
Geometric Mean Titer (GMT)	32.4 (25.4-41.4)	41.7 (32.8-53.0)	REF	46.0 (34.8-60.8)	56.8 (43.3-74.6)	0.021	44.4 (34.9-56.5)	62.0 (49.0-78.4)	**0.002**	40.3 (31.5-51.4)	78.9 (62.2-100.2)	**<0.001**
Mean-fold Rise in GMT	–	1.3 (1.1-1.5)	REF	–	1.2 (1.0-1.5)	0.663	–	1.4 (1.2-1.6)	0.344	–	2.0 (1.7-2.3)	**<0.001**
HI titer ≥1:40	–	75% (64-87%)	REF	–	78% (67-92%)	0.530	–	82% (73-93%)	0.189	–	86% (78-96%)	0.034
HI titer ≥1:80	–	33% (23-49%)	REF	–	48% (35-66%)	0.040	–	54% (42-69%)	**0.004**	–	60% (49-75%)	**<0.001**
HI titer ≥1:160	–	8% (3-20%)	REF	–	20% (11-37%)	0.020	–	23% (14-37%)	**0.006**	–	37% (26-52%)	**<0.001**
B/Yamagata												
Seroconversion Rate (SCR)	–	4% (1-15%)	REF	–	5% (1-19%)	0.712	–	10% (5-22%)	0.086	–	35% (24-50%)	**<0.001**
Geometric Mean Titer (GMT)	40.3 (30.1-53.8)	53.6 (40.2-71.5)	REF	28.2 (20.2-39.2)	34.2 (24.6-47.4)	**0.005**	48.0 (36.1-63.9)	66.2 (49.9-87.8)	0.157	48.3 (36.2-64.5)	113.5 (85.2-151.2)	**<0.001**
Mean-fold Rise in GMT	–	1.3 (1.1-1.6)	REF	–	1.2 (1.0-1.5)	0.393	–	1.4 (1.1-1.7)	0.726	–	2.4 (1.9-2.8)	**<0.001**
HI titer ≥1:40	–	77% (67-89%)	REF	–	56% (42-73%)	**0.004**	–	75% (64-87%)	0.622	–	92% (85-100%)	**0.004**
HI titer ≥1:80	–	48% (36-63%)	REF	–	27% (16-44%)	**0.006**	–	58% (46-72%)	0.173	–	79% (68-90%)	**<0.001**
HI titer ≥1:160	–	20% (11-34%)	REF	–	15% (7-31%)	0.443	–	35% (24-50%)	0.016	–	56% (45-71%)	**<0.001**

HD-IIV3: high-dose trivalent inactivated influenza vaccine represented by Fluzone® High-Dose by Sanofi Pasteur; SD-IIV4: standard dose quadrivalent inactivated influenza vaccine represented by Fluzone® Quadrivalent by Sanofi Pasteur; ccIIV4: cell-culture based inactivated influenza vaccine represented by Flucelvax Quadrivalent™ by Seqirus; RIV4: recombinant inactivated influenza vaccine represented by Flublok® Quadrivalent by Sanofi Pasteur; HI: hemagluttination inhibition.

† Hemagglutination inhibition antibody titers were measured against the following cell-grown vaccine reference viruses: A/Kansas/14/2017 (H3N2); A/Idaho/07/2018 (H1N1) pdm09 (A/Brisbane/02/2018-like), B/Colorado/06/2017 (B/Victoria) and B/Phuket/3073/2013 (B/Yamagata) viruses.

‡The per protocol population comprised eligible HCP who received study vaccine and had sera drawn and tested at around one-month post-vaccination within the protocol-specified acceptable time interval (20-62 days post-vaccination).

[a]Day 0 and one-month unadjusted outcomes with 99.3% CIs.

[b]p-values based on unadjusted logistic regression and ANOVA models comparing HD-IIV3, ccIIV4, and RIV4 to SD-IIV4 as the referent group. A Bonferroni correction for multiple comparisons was prespecified in the protocol for seven comparisons of different combinations of influenza vaccines during the two trial seasons (three presented here and four in another report). Therefore, statistical significance was defined at p=0.007.

Supplemental Table 2. Geometric mean titer ratios adjusted for the log of pre-vaccination titers and study site at one month post-vaccination by hemagglutination inhibition† by recipients of high-dose egg-based, cell culture-based, and recombinant influenza vaccines compared to recipients of standard-dose egg-based influenza vaccine, Kaiser Permanente Northwest participants only

	HD-IIV3			ccIIV4			RIV4		
	Adjusted GMT Ratio[a]	99.3% CI	P-value[b]	Adjusted GMT Ratio[a]	99.3% CI	P-value[b]	Adjusted GMT Ratio[a]	99.3% CI	P-value[b]
A/H1N1	1.0	(0.8-1.3)	0.965	1.2	(0.9-1.6)	0.159	1.4	(1.0-1.9)	0.010
A/H3N2	1.2	(0.8-1.8)	0.289	0.9	(0.5-1.3)	0.326	1.9	(1.2-2.9)	**<0.001**
B/Victoria	1.1	(0.8-1.4)	0.577	1.1	(0.8-1.5)	0.349	1.5	(1.1-2.0)	**<0.001**
B/Yamagata	0.8	(0.6-1.2)	0.151	1.0	(0.7-1.5)	0.979	1.7	(1.2-2.5)	**<0.001**

HD-IIV3: high-dose trivalent inactivated influenza vaccine represented by Fluzone® High-Dose by Sanofi Pasteur; SD-IIV4: standard dose quadrivalent inactivated influenza vaccine represented by Fluzone® Quadrivalent by Sanofi Pasteur; ccIIV4: cell-culture based inactivated influenza vaccine represented by Flucelvax Quadrivalent™ by Seqirus; RIV4: recombinant inactivated influenza vaccine represented by Flublok® Quadrivalent by Sanofi Pasteur.

† Hemagglutination inhibition antibody titers were measured against the following cell-grown vaccine reference viruses: A/Kansas/14/2017 (H3N2); A/Idaho/07/2018 (H1N1)pdm09 (A/Brisbane/02/2018-like), B/Colorado/06/2017 (B/Victoria) and B/Phuket/3073/2013 (B/Yamagata) viruses.

[a] Ratio of geometric mean titers at one month post-vaccination, adjusted for study site and the log of prevaccination titers, among HD-IIV3 recipients, ccIIV4 recipients or RIV4 recipients compared to SD-IIV4 recipients.

[b] p-values based on ANOVA models adjusted for study site and the log of pre-vaccination titers comparing HD-IIV3, ccIIV4, and RIV4 to SD-IIV4 as the referent group. A Bonferroni correction for multiple comparisons was prespecified in the protocol for seven comparisons of different combinations of influenza vaccines during the two trial seasons (three presented here and four in another report). Therefore, statistical significance was defined at p=0.007.