SUPPLEMENTARY MATERIAL

Comparative Immunogenicity of Enhanced Influenza Vaccines in Older Adults: A Randomized Controlled Trial

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1. Study design

This randomized trial was designed to evaluate the strength and duration of immune responses between annual receipt of standard dose influenza vaccine and alternative enhanced influenza vaccines, including annual receipt of MF59-adjuvanted vaccine, annual receipt of high-dose vaccine, annual receipt of recombinant HA vaccine, and alternating combinations of enhanced and/or standard dose vaccines, over four years. The overall aim of the study is to provide scientific evidence to support improved influenza vaccination strategies in older adults.

Because we intend to examine alternative combinations of repeated vaccination with standard dose and enhanced vaccines in this trial, we randomized participants to 11 different groups in equal proportions. In year 1, the first three of 11 equally sized groups (i.e. 27% of participants) all received standard dose quadrivalent IIV (0.5mL FluQuadri, Sanofi Pasteur containing 60μg HA, 15μg for each influenza strain included). Groups 4-6 received trivalent MF59-adjuvanted IIV (0.5 mL FLUAD, Seqirus, containing 45μg HA; 15μg for each influenza strain included, and MF59C.1 adjuvant). Groups 7-9 received trivalent high-dose IIV (0.5mL Fluzone High-Dose, Sanofi Pasteur, containing 180μg HA; 60μg for each influenza strain included). Participants in group 10 and 11 received quadrivalent recombinant-HA vaccine (0.5mL Flublok, Sanofi Pasteur, containing 180μg HA, 45μg for each influenza strain included). This design is shown in **Appendix Figure 1** below. After randomization, there are four main categories of strategies, which are described in **Appendix Table 1**. We used R software to generate the allocation sequence. We used a block randomization structure with randomly permuted block sizes of 11 and 22.

	Round 1 2017-18	Round 2 2018-19	Round 3 2019-20	Round 4 2020-21
Group I	QIV	QIV	QIV	QIV
Group II	QIV	MF59-adj TIV	QIV	MF59-adj TIV
Group III	QIV	High-dose TIV	QIV	High-dose TIV
Group IV	MF59-adj TIV	QIV	MF59-adj TIV	QIV
Group V	MF59-adj TIV	MF59-adj TIV	MF59-adj TIV	MF59-adj TIV
Group VI	MF59-adj TIV	High-dose TIV	MF59-adj TIV	High-dose TIV
Group VII	High-dose TIV	QIV	High-dose TIV	QIV
Group VIII	High-dose TIV	MF59-adj TIV	High-dose TIV	MF59-adj TIV
Group IX	High-dose TIV	High-dose TIV	High-dose TIV	High-dose TIV
Group X	Recombinant HA QIV	Recombinant HA QIV	Recombinant HA QIV	Recombinant HA QIV
Group XI	Recombinant HA QIV	MF59-adj TIV	Recombinant HA QIV	MF59-adj TIV

Appendix Figure 1: Study design including 11 intervention groups during the four-year trial. Analysis in this report focuses on year 1 only.

Appendix Table 1: Categories of influenza vaccination strategies considered in this trial, and the corresponding group number and target sample size in year 1. *Group numbers and row colours correspond to those shown in Appendix Figure 1.*

Category	**Vaccine administered**	**Group**	**Participants in Year 1**
Comparator	Standard QIV	I	200
Repeated used of the same enhanced vaccine	MF59-adj TIV	V	200
	High-dose TIV	IX	200
	Rec-HA QIV	X	200
Alternating use of an enhanced vaccine and standard dose vaccine	Standard QIV, MF59-adj TIV	II	200
	MF59-adj TIV, Standard QIV	IV	200
	Standard QIV, High-dose TIV	III	200
	High-dose TIV, Standard QIV	VII	200
Alternating use of two enhanced vaccines	MF59-adj TIV, High-dose TIV	VI	200
	High-dose TIV, MF59-adj TIV	VIII	200
	Rec-HA QIV, MF59-adj TIV	XI	200

By including combination strategies in this trial, we will obtain information on the safety and immunogenicity of repeat administration of enhanced vaccines. This study may also provide evidence on the potential advantages of alternating vaccination strategies using different enhanced vaccines with slightly different biological mechanisms. However for this report, we focus on the results in year 1, including four groups namely standard dose (groups 1-3), MF59-adjuvanted vaccine (groups 4-6), high dose vaccine (groups 7-9), and recombinant-HA vaccine (groups 10-11).

1.1 Collection of blood samples from study participants

We collected 9mL blood specimens from each participant at the baseline visit before receipt of vaccine, at 30 days after vaccination, and at 6 months after vaccination. We selected 10% of the participants for additional blood draws throughout the study, by inviting each participant upon recruitment in the first round of the study until a maximum of 220 participants was reached in this subset. This subset of participants were invited to provide an additional 9mL blood specimen at 3 months and 9 months after vaccination for serologic testing, and an additional 20mL blood specimen at baseline, 7 days and 30 days after vaccination in heparinized tubes for analysis of cell-mediated immunity, and an additional 20 mL blood specimen 6 months after vaccination in EDTA tubes for host genetic testing including HLA typing.

The analysis presented in the main text relates only to the analysis of blood samples collected at day 0, day 7 and day 30 in the first year of this trial, in which we are able to compare the immunogenicity of the three enhanced vaccines with the standard dose group. Results for subsequent time points and subsequent years will be reported in due course.

1.2 Sample size justification

We aimed to enrol 2200 participants into our study, as this would permit us to have a sample size of at least 1604 participants (with 146 participants in each group) at the fourth year of follow-up allowing for 10% drop-out per year without replacement. The sample size calculation was based on comparisons between the standard dose group and the other groups in years 2-4, aiming for 80% power to detect ≥17% difference in participants who achieved the targeted rise and 1.5-fold difference in post-vaccination GMTs, assuming a standard deviation of $\log_2$(GMT) of 1.7.[1] In year 1 we were able to enrol 1861 participants, which was somewhat below our target sample size, and may have implications for study power if there are fewer than 146 participants per group in year 4.

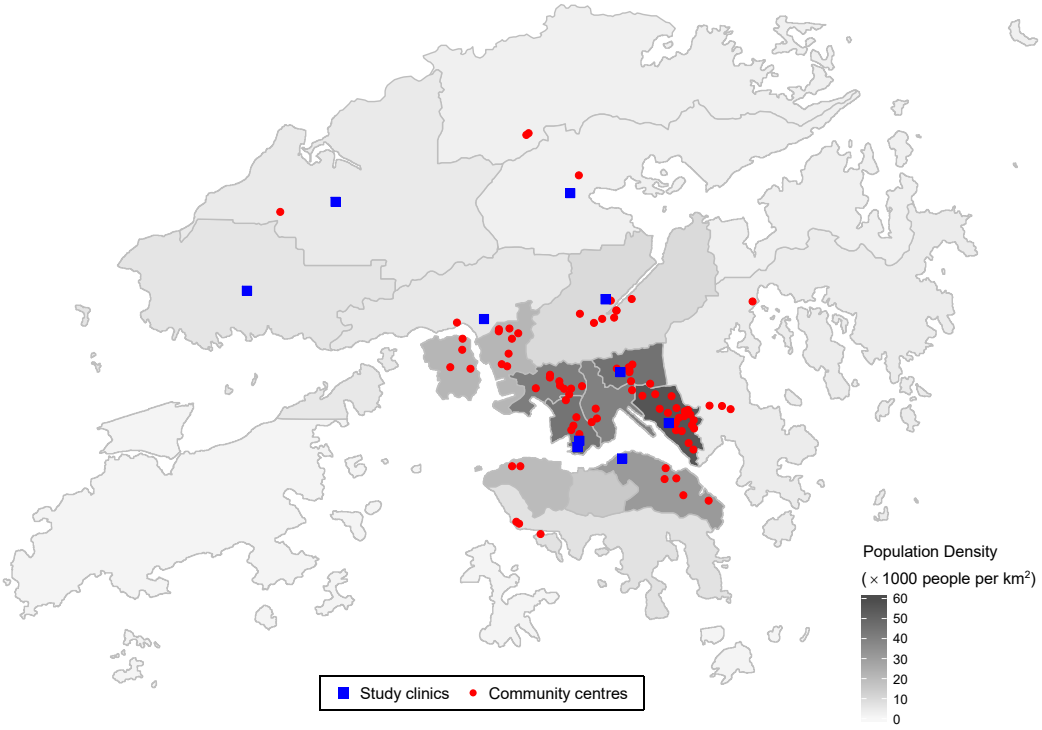
2. Additional details on enrolment strategies

We enrolled community-dwelling older adults who were: (1) 65-82 years of age, (2) residing in Hong Kong, and (3) had not already received northern hemisphere 2017/18 formulation of influenza vaccination. Participants were ineligible to participate if they: (1) showed signs of dementia[2] or had a clinical diagnosis of dementia or other significant cognitive impairment; (2) reported medical conditions not suitable to receive an IIV[3] such as any documented Guillain-Barre syndrome within 6 weeks of previous vaccination, or any documented allergic reaction to egg protein or previous dose of influenza vaccine; (3) reported medical conditions not suitable to receive intramuscular injection such as habitual use of anticoagulant medication (other than antiplatelet medication such as aspirin); (4) had any medical condition rendering them not suitable to receive IIV as determined by a clinician.

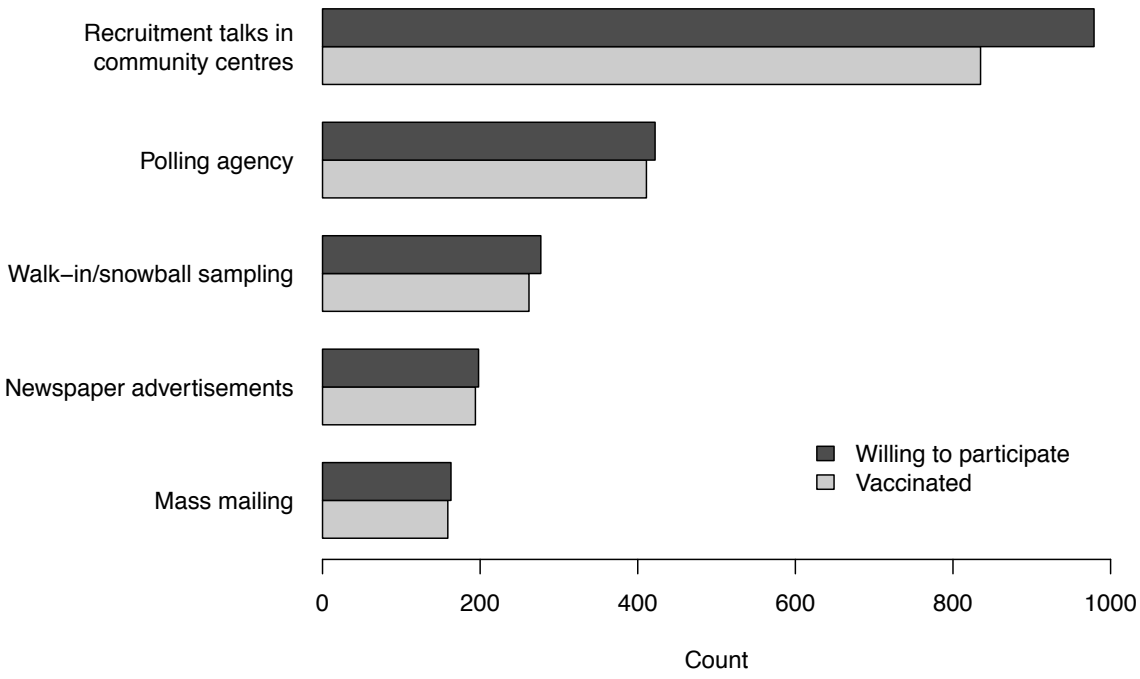
We began enrolment in June 2017, partnering with local community centers and arranging health talks that concluded with an introduction to our trial. Interested older adults were

provided with further information about the study and screened to determine if they met eligibility criteria. The screening process included the Mini-Cog test[2] to ensure that interested older adults had no signs of dementia or significant cognitive impairment. In September 2017 we expanded recruitment efforts including: (1) advertising our study by mass mailing to public and private residential estates and senior citizen residences; (2) advertising in local newspapers, websites with older adults as target audience, and our own study website; (3) by engaging a local polling agency to contact local older adults and introduce our study to them; and (4) by snowball sampling through various channels, including inviting participants in this study to refer their friends to us, and by advertising the study to participants or screened individuals from our other prior studies or events who had consented to receive information about new studies. From these sources, participants showing interest were screened by telephone, and eligible individuals were then invited to meet in person at community centers or designated study clinics to provide further information and to obtain signed informed consent. After consent, study staff completed a brief interview with each participant to collect relevant baseline information. We began to administer study vaccinations in October 2017.

From 28 June 2017 through 18 December 2017 we conducted 134 health talks in 81 local community centers (**Appendix Figure 2**), screening 1348 older adults of whom 1254/1348 (93%) were eligible, and 979/1254 (78%) agreed to participate. In the expanded recruitment approaches from 12 July 2017 through 11 January 2018, we were able to screen 1797 older adults of whom 1441/1797 (80%) were eligible and 1060/1441 (74%) agreed to participate. The breakdown of sources of these participants is shown in **Appendix Figure 3**.



Appendix Figure 2: Location of study clinics and community centres where we conducted enrolment activities, compared to the overall population density in Hong Kong.



Appendix Figure 3: Sources of participants enrolled in the trial.

2.1 Selection of 800 participants for serologic analyses

We selected pairs of samples from 800 participants, including 200 who had received each of the four vaccines, to evaluate humoral immune responses to vaccination.

Appendix Table 2: Baseline characteristics of the 166 participants who provided extra blood and with serology results available, by vaccination group.

Characteristics	Vaccination group			
	Standard dose QIV (N=53/499)	**MF59-adjuvanted TIV (N=45/500)**	**High dose TIV (N=41/505)**	**Recombinant-HA high dose QIV (N=27/322)**
	n (%)	n (%)	n (%)	n (%)
Age, in years				
65-70	32 (60%)	20 (44%)	28 (68%)	14 (52%)
71-76	10 (19%)	16 (36%)	7 (17%)	6 (22%)
77-82	11 (21%)	9 (20%)	6 (15%)	7 (26%)
Female sex	33 (62%)	30 (67%)	26 (63%)	13 (48%)
Underlying medical conditions				
Hypertension	27 (51%)	27 (60%)	18 (44%)	17 (63%)
Osteoarthritis	14 (26%)	9 (20%)	5 (12%)	12 (44%)
Diabetes	16 (30%)	10 (22%)	7 (17%)	4 (15%)
Heart diseases	8 (15%)	2 (4%)	5 (12%)	3 (11%)
Cancer	8 (15%)	4 (9%)	4 (10%)	3 (11%)
Others	22 (42%)	23 (51%)	19 (46%)	11 (41%)
Received influenza vaccination in 2016/17 season	31 (58%)	28 (62%)	26 (63%)	19 (70%)
No. of times received influenza vaccination in the past 5 years*				
0	16 (30%)	12 (27%)	14 (34%)	7 (26%)
1-2	10 (19%)	9 (20%)	3 (7%)	3 (11%)
3-4	7 (13%)	6 (13%)	5 (12%)	3 (11%)
5-6	18 (34%)	16 (36%)	19 (46%)	13 (48%)

*including northern hemisphere formulations of influenza vaccines from 2012/13 through 2016/17 and the southern hemisphere formulation of the influenza vaccine in 2015.

We first selected all 166 participants from the subset of participants who provided additional blood samples (53, 45, 43 and 27 in the four groups), and then we drew a random sample of 634 participants without replacement based on the following criteria: (1) had both day 0 and day 30 sera; (2) total number of participants in each of the four vaccine groups was ≤200. By this approach we selected a total of 800 participants for serologic testing, and the characteristics of the 800 selected participants are shown in **Appendix Table 2** above. The baseline characteristics were very closely matched between groups, with no statistically significant differences.

3. Monitoring adverse events following vaccination

After vaccination, participants were observed for 15 minutes for acute reactions. Participants were then called by telephone four times after vaccination, on days 1-2, 3-4, 7-9 and 14-16 respectively, for recording of local or systemic adverse reactions. Ranges of 2-3 days were permitted for each of these calls to allow for flexibility in scheduling, and to mitigate potential difficulties in contacting participants on weekends.

Participants were also encouraged to call the study hotline number listed on the vaccination card to contact our research team for medical advice if they experienced any possible adverse reactions to vaccination including fever, muscle pain, nausea, fatigue, and local site reactions including redness, swelling, tenderness, itching, and pain at injection site.[4,5] Possible adverse reactions were graded according to severity: a mild adverse event was one in which the symptoms were easily tolerated and did not interfere with usual activities; a moderate reaction caused interference with usual activities, and a severe reaction resulted in inability to perform usual activities. For swelling and erythema, we used quantitative classification of mild/moderate/severe reactions as follows: “mild” if the diameter of the maximum reaction

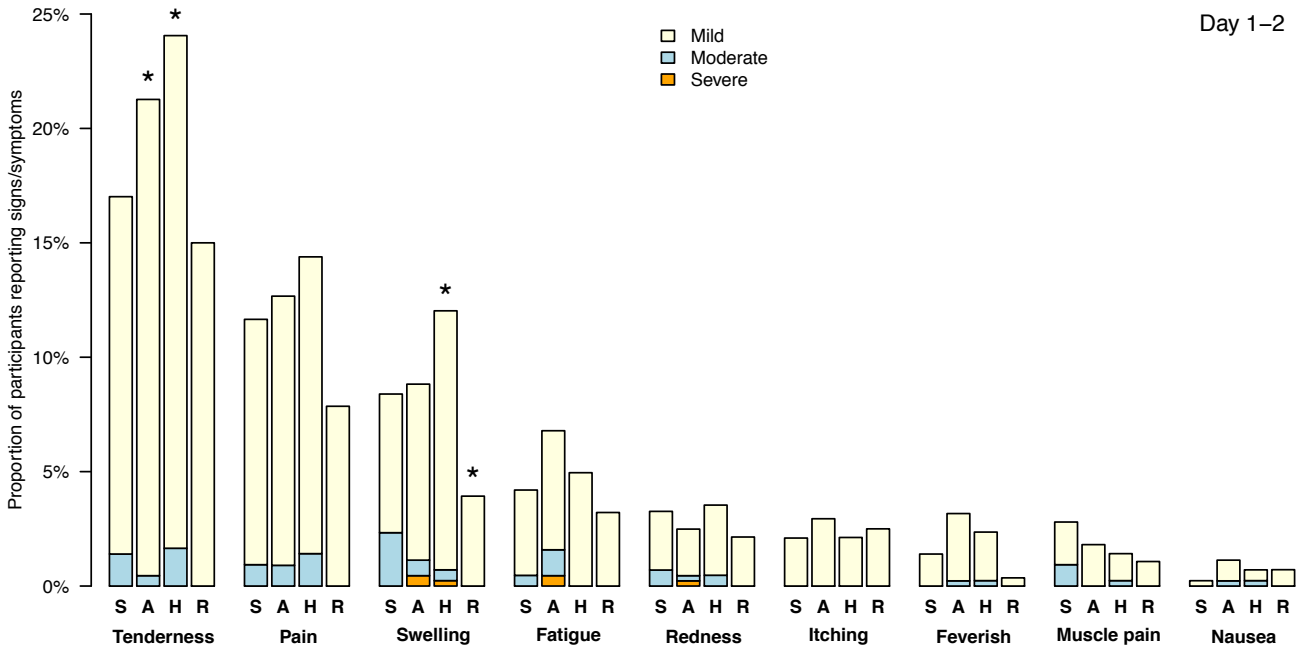
size was <2.5 cm; “moderate” if the diameter of the maximum reaction size was between 2.5 and 5cm; and “severe” if the diameter of the maximum reaction size was ≥5 cm.

In addition, during the visit for blood collection at 30 days after vaccination, information on any possible serious adverse events (SAEs) in the past 30 days was collected from all participants. An SAE is any undesirable experience associated with the use of a medical product in participant when the outcome is either: 1) death; 2) life-threatening; 3) hospitalization; 4) disability or permanent damage; 5) required intervention to prevent permanent impairment or damage or 6) other serious medical event.

Patterns in acute events after vaccination are shown in **Appendix Figure 4**. Rates of adverse events in recipients of enhanced vaccines were generally comparable to recipients of the standard dose vaccine, with slightly higher rates of tenderness in recipients of the MF59-adjuvanted vaccine and the high-dose vaccine, higher rates of swelling in the high-dose group, and significantly lower rates of swelling in the recombinant-HA vaccine group.

Appendix Table 3: Comparisons of participants reporting hospitalizations among four vaccination groups.

Hospitalizations	**Vaccination group**							
	Standard dose QIV (N=508)		**MF59-adjuvanted TIV (N=508)**		**High dose TIV (N=510)**		**Recombinant-HA high dose QIV (N=335)**	
	n	(%)	n	(%)	n	(%)	n	(%)
Overall	41	(8.1%)	47	(9.3%)	36	(7.1%)	22	(6.6%)
Time since vaccination								
<1 month	7	(1.4%)	3	(0.6%)	5	(1.0%)	2	(0.6%)
1-3 months	9	(1.8%)	13	(2.6%)	7	(1.4%)	4	(1.2%)
4-6 months	20	(3.9%)	24	(4.7%)	13	(2.5%)	14	(4.2%)
>6 months	1	(0.2%)	3	(0.6%)	2	(0.4%)	0	(0.0%)



Appendix Figure 4: Reactions reported by 1575/1861 (85%) participants who were successfully reached for the follow-up call on day 1 or 2 after vaccination*. Rates of events that differed significantly from the rate in the corresponding standard dose group are indicated with asterisks. Abbreviations: S = standard dose vaccine; A = MF59-adjuvanted vaccine; H = high-dose vaccine; R = recombinant-HA vaccine.*

5. Additional information on serologic assays and results

Pairs of day 0 and day 30 sera from participants were tested by hemagglutination inhibition (HAI) assays against egg-propagated vaccine strains A/Singapore/GP1908/2015 (A/Michigan/45/2015 (H1N1) pdm09- like virus), A/Hong Kong/4801/2014(H3N2), B/Brisbane/60/2008 and B/Phuket/3073/2013. The influenza B antigens were ether split. In addition we tested sera by virus microneutralization (MN) against cell-propagated A/Hong Kong/4801/2014(H3N2).

The HAI assay was carried out as described previously,[6] using "V" bottomed micro titer plates. Briefly, the test sera were first RDE treated and subsequently inactivated at 56°C for

30 min. Fifty microliters of each sample was serially diluted in a 96 well format containing 25µL phosphate buffered saline. This was followed by the addition of 25µL of four hemagglutinating units (HAU) the antigen and an incubation for 1hr at room temperature. Fifty microlitres of 0.5% turkey red blood cells (LAMPIRE Biological Laboratories, (USA) Cat: 7209403) was added to each well. Plates were then incubated at room temperature for 30 min. The titers were recorded as the reciprocal of the highest serum dilution that completely inhibited hemagglutination. Oseltamivir was not included in any of the HAI assays.

The MN assay was carried out as described previously,[7] with modifications as below. Two-fold dilutions of heat-inactivated sera starting with a dilution of 1:10 was prepared in 96-well format. The serum dilutions were mixed with equal volumes of 200 $TCID_{50}$ of A/Hong Kong/4801/2014(H3N2) that had been grown in MDCK cells from the original clinical specimen to avoid egg adaptations (Appendix Table 4). The plates were incubated at 37°C, for 1 hour and then 35µL of the virus–serum mixture was added in quadruplicate to MDCK cell monolayers in 96-well microtiter plates. They were incubated for 1 hour in a 37°C humidified incubator, then the supernatant was discarded, washed and 150 µL of culture medium (0% minimal essential medium with TPCK trypsin) were added to each well. The plates were incubated for three more days at 37°C in 5% CO_2 in a humidified incubator. Cytopathic effect was read at three days post infection. The highest serum dilution that showed 50% protection was taken as the neutralising antibody titre and was estimated using the Reed-Muench method.[8] Positive and negative control sera were included to validate the assay. A virus back-titration was performed with each assay without immune serum to confirm the input virus dose.

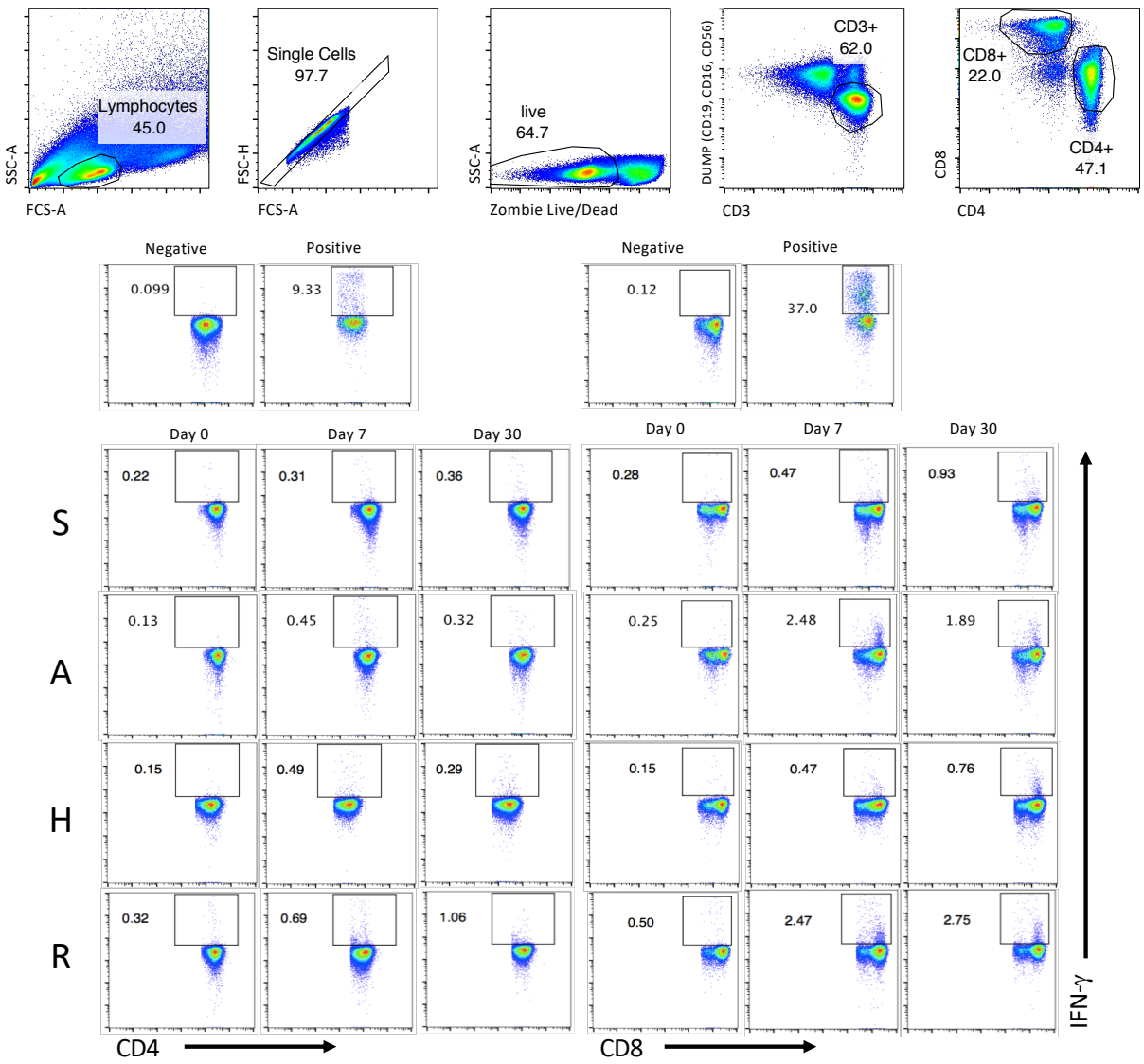
Appendix Table 4: Details of viruses used in serology assays

Assay	Antigen/Virus	GISAID ID	Notes
Hemagglutination inhibition	A/Singapore/GP1908/2015 (A/Michigan/45/2015(H1N1) like virus)	EPI1140337	Antigen grown in eggs
Hemagglutination inhibition	A/HongKong/4801/2014 (H3N2)	EPI578430	Antigen grown in eggs
Hemagglutination inhibition	B/Brisbane/60/2008 (Victoria lineage)	EPI173277	Antigen grown in eggs
Hemagglutination inhibition	B/Phuket/3073/2013 (Yamagata lineage)	EPI539767	Antigen grown in eggs
$TCID_{50}$ microneu-tralization	A/Hong Kong/4801/2014 (H3N2)	EPI1312170	Antigen grown in cells, does not have egg adaptations

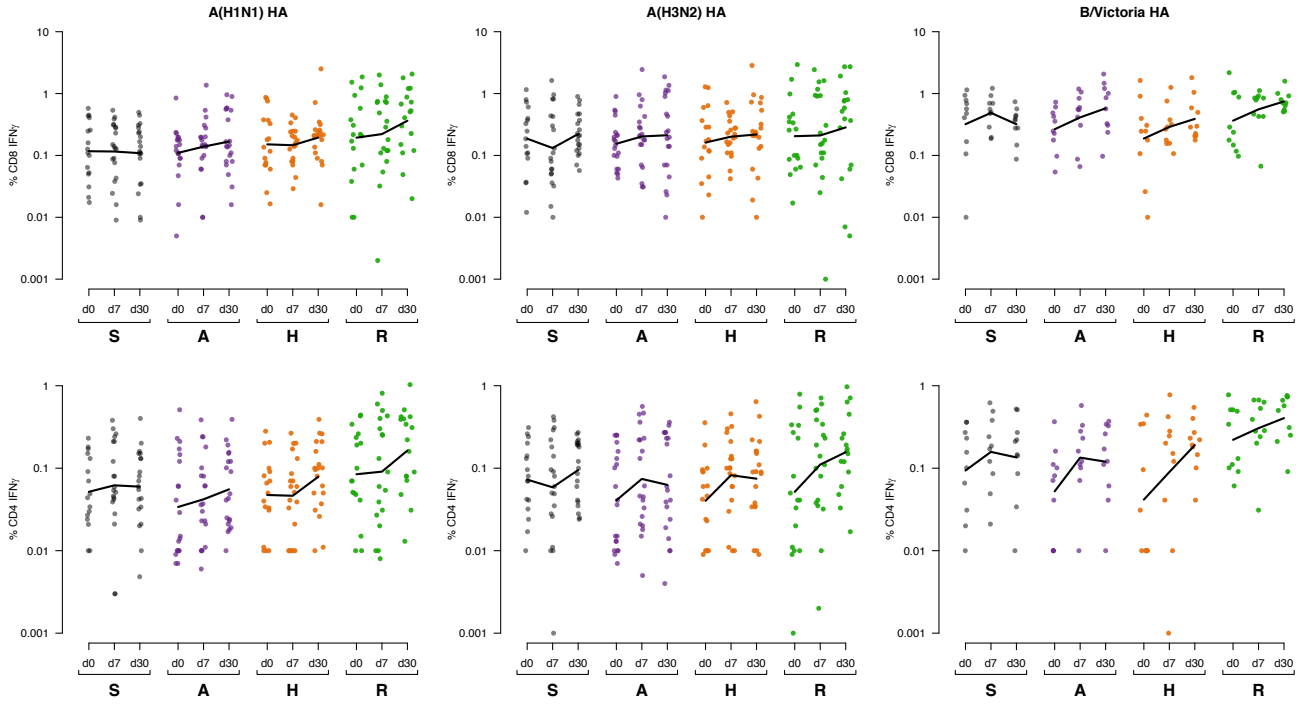
6. Additional information on cell-mediated immunity assays and results

We randomly selected 20 participants in each group for analysis of cellular immunity with complete time-points, from the same subjects used for serology analysis. Influenza-specific $CD4^+$ and $CD8^+$ T cell responses were assessed by IFN-γ^+ production by flow cytometry.[9] Briefly, $4x10^6$ PBMCs from equivalent 5ml blood, were thawed in cRMPI (RPMI 1640 supplemented with 2 mM L-glutamine, 1 mM sodium pyruvate, 100 mM non-essential amino acids, 5 mM Hepes buffer, 55 mM 2-metactoethanol, 100 U/ml Penicillin, 100 mg/ml streptomycin, plus 10% v/v Heat-Inactivated Fetal Calf Serum (HI-FCS)) with Benzoase (1:5,000, Merck). Thawed cells had an average cell viability of 75%. Cells were washed twice and resuspended in the 300µl of cRPMI with no FBS, in 96 well U-bottom Costar TC treated plates. PBMCs were restimulated with MOI 4 of UV-inactivated (10 minute exposure, 10,000

J) influenza viruses: A/California/04/2009 (H1N1), A/Switzerland/9715293/2013 (H3N2), and B/Brisbane/6/2008 (Victoria-lineage), with purified CD28, CD49d (Biolegend) and IL-2 (Roche). UV inactivated virus was used to present virus derived epitopes and access to MHC-I and II machinery without cell death of antigen presenting cells. At 4 hours, BFA and Monensin (BD) were added, and incubated for a further 12 hours. Cells were stained with viability dye, Zombie-NIR (Biolegend) in PBS, then further stained for anti-human CD14/CD19/CD16-BV510, CD3-PETexas, CD4-BV605 and CD8-AF700 (Biolegend). Cells were fixed with Cytofix/cytoperm buffer (BD), and stained for anti-human IFN-γ-FITC (Biolegend) in Perm wash buffer (BD). Cells were assessed by flow cytometry on an Invitrogen Attune and analysed on FlowJo software (see **Appendix Figure 5** for FACS gating strategy and representative FACS plots). IFN-γ from background media alone controls were subtracted from each sample. Positive controls included PMA/Ionomycin stimulation, and 10 donors isolated from buffy packs as internal assay controls. Raw data on influenza-specific $CD4^+$ and $CD8^+$ T cell responses on days 0, 7 and 30, are shown in **Appendix Figure 6**, and the ratios of day 7 / day 0 and day 30 / day 0 are presented in Figure 2 in the main text and in **Appendix Table 5** below. That table also includes ratios of day 30 / day 7 responses, representing the rate of contraction of peak acute responses to long term-memory.



Appendix Figure 5: Assessment of IFN-γ+ CD4+ and CD8+ T cells by flow cytometry*. The kinetics of influenza strain-specific CD4+ and CD8+ T cells, after receipt of standard dose (S), MF59-adjuvant (A), high dose (H) and recombinant-HA (R) vaccines, were determined by stimulation with whole virus for IFN-γ+ production by ICS FACS assay. The gating strategy of lymphocytes, doublet exclusion, live cells, CD3+ dump- (CD56, CD16, CD19), CD4/CD8+ and IFN-γ+. Representative FACS plots are shown for positive controls (PMA/ionomycin), negative (no virus) for CD4+ and CD+8 IFN-γ+ T cells. The fold change of day 7 and 30 IFN-γ+ T cells from baseline day 0 pre-vaccination responses was calculated for each virus after in vitro stimulation for CD8+ and CD4+ IFN-γ+ T cells.*



Appendix Figure 6: Influenza specific T cell responses of standard dose and enhanced vaccine recipients. *(top panel) CD8⁺ IFN-γ⁺ and (bottom panel) CD4⁺ IFN-γ⁺ T cell responses for H1N1, H3N2, and B/Victoria viruses, after vaccination (baseline d0, acute d7, memory d30 time-points) with standard dose (S), MF59-adjuvant (A), high dose (H) and recombinant-HA (R). Data represents the individual subject response (n=20) and group mean. FACS gating strategy shown in Appendix Figure 6.*

Appendix Table 5: *CD8⁺ and CD4⁺ IFN-γ⁺ T cells response magnitude fold change increases (D7/D0 and D30/D0) following vaccination and fold change decreases after acute vaccination timepoint (D30/D7) (from Appendix figure 7).*

	Vaccination group							
	Standard dose QIV (N=20)		**MF59-adjuvanted TIV (N=20)**		**High dose TIV (N=20)**		**Recombinant-HA QIV (N=20)**	
	Est	(95% CI)	Est	(95% CI)	Est	(95% CI)	Est	(95% CI)
Fold change (CD8⁺ IFN-γ⁺)								
A/California/04/2009 (H1N1)								
D7/D0	1.02	(0.64, 1.63)	1.26	(0.72, 2.20)	1.15	(0.74, 1.79)	1.38	(0.73, 2.60)
D30/D0	1.02	(0.61, 1.71)	1.53	(0.89, 2.62)	1.36	(0.79, 2.33)	1.95	(1.13, 3.37)
D30/D7	0.94	(0.52, 1.69)	1.21	(0.74, 1.97)	1.33	(0.91, 1.69)	1.19	(0.73, 1.93)
A/Switzerland/9715293/2013 (H3N2)								
D7/D0	0.85	(0.44, 1.65)	1.31	(0.76, 2.26)	1.28	(0.79, 2.09)	1.40	(0.57, 3.39)
D30/D0	1.33	(0.71, 2.52)	1.37	(0.68, 2.79)	1.45	(0.70, 3.01)	1.75	(0.82, 3.75)
D30/D7	1.68	(0.91, 3.13)	1.05	(0.64, 1.70)	1.08	(0.65, 3.13)	1.16	(0.57, 2.38)
B/Brisbane/60/2008								
D7/D0	1.53	(0.67, 3.50)	1.55	(0.69, 3.51)	1.54	(0.84, 2.82)	1.53	(0.73, 3.21)
D30/D0	1.00	(0.46, 2.19)	2.18	(1.05, 4.52)	2.08	(0.88, 4.90)	2.05	(1.10, 3.82)
D30/D7	0.65	(0.45, 0.96)	**1.40**	**(0.93, 2.12)**	**1.35**	**(0.93, 0.96)**	**1.34**	**(0.85, 2.12)**
Fold change (CD4⁺ IFN-γ⁺)								
A/California/04/2009 (H1N1)								
D7/D0	1.81	(1.19, 2.75)	1.24	(0.76, 2.02)	1.03	(0.48, 2.22)	1.30	(0.84, 2.02)
D30/D0	1.19	(0.80, 1.79)	1.64	(0.97, 2.76)	1.61	(0.90, 2.90)	2.00	(1.34, 2.99)
D30/D7	0.96	(0.53, 1.74)	1.32	(0.83, 2.11)	1.70	(0.96, 1.74)	1.25	(0.97, 1.60)
A/Switzerland/9715293/2013 (H3N2)								
D7/D0	1.20	(0.73, 1.97)	1.82	(1.09, 3.03)	2.04	(0.97, 4.28)	2.59	(1.11, 6.05)
D30/D0	1.40	(0.85, 2.31)	1.54	(0.82, 2.90)	2.23	(1.08, 4.60)	3.23	(1.44, 7.24)
D30/D7	1.62	(0.83, 3.17)	0.85	(0.55, 1.30)	0.91	(0.62, 3.17)	1.16	(0.69, 1.94)
B/Brisbane/60/2008								
D7/D0	1.68	(0.76, 3.74)	2.56	(1.60, 4.11)	2.16	(0.75, 6.24)	1.38	(0.76, 2.53)
D30/D0	1.44	(0.85, 2.43)	2.29	(1.22, 4.31)	4.58	(1.73, 12.1)	1.83	(1.12, 3.00)
D30/D7	0.86	(0.35, 2.11)	0.89	(0.63, 1.26)	2.12	(0.61, 2.11)	1.32	(0.84, 2.10)

Bold indicates a significant difference compared to the response in the standard dose vaccine group at the same timepoint
Underlined values indicates a significant difference compared to the baseline response within the same vaccine group.

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