Supplemental Table 1. Baseline characteristics of the study population

	Transcutaneous route (n=20)	**Intradermal route (n=20)**	**Intramuscular route (n=20)**	**P value**
Female, n (%)	13 (65%)	10 (50%)	13 (65%)	0.67
Age, years (interquartile range)	32.5 (28–40.5)	32.5 (28–38)	27.5 (24–35)	0.16
Body mass index, kg/m^2 (interquartile range)	23.3 (22.1–24.6)	23.6 (22.9–25.1)	23.5 (22.2–24.9)	0.56
History of inflammatory, autoimmune, or chronic disease, n (%)	4 (20%)	4 (20%)	5 (25%)	1
Anti-inflammatory treatment, n (%)	0 (0%)	1 (5%)	1 (5%)	1
Received at least one seasonal influenza vaccination (2009–2012), n (%)	7 (35%)	15 (75%)	8 (40%)	0.0340*
Received A(H1N1)pdm09 influenza vaccine, n (%)	6 (30%)	14 (70%)	6 (30%)	0.0177*

The Vaxigrip® (0.5 mL/dose) and Intanza®15 (0.1 mL/dose) vaccines each contained 15 µg of hemagglutinin (HA) from split-inactivated influenza virus from each of the three strains: A/California/7/2009 (H1N1)pdm09-like strain, A/Victoria/361/2011 (H3N2)-like strain, and B/Wisconsin/1/2010-like strain. Means (percentages within the group) or medians (interquartile range) are shown. Kruskal-Wallis tests or Fisher's exact tests were performed to compare characteristics between the three groups (* P-value<0.05).

Supplemental Table 2. Local and systemic reactions induced within the first 5 days of vaccination according to the route of vaccination

	Transcutaneous route (n=20)				Intradermal route (n=20)				Intramuscular route (n=20)				
	Mild	**Moderate**	**Severe**	**Total**	**Mild**	**Moderate**	**Severe**	**Total**	**Mild**	**Moderate**	**Severe**	**Total**	**p-value**
At least one local reaction, (%)				13 (65%)				20 (100%)				14 (70%)	0.0078
Erythema	11	0	0	11	17	3	0	20	2	0	0	2	<0.0001
Pruritus	2	0	0	2	2	1	0	3	0	0	0	0	ns
Pain	0	0	0	0	8	1	0	9	12	0	0	12	<0.0001
Induration	0	0	0	0	13	1	0	14	0	0	0	0	<0.0001
Swelling	0	0	0	0	7	0	0	7	0	1	0	1	0.0038
Eczema	0	0	1[a]	1	0	0	0	0	0	0	0	0	ns
Local dysesthesia	2	0	0	2	2	0	0	2	1	0	0	1	ns
At least one systemic reaction, n (%)				11 (55%)				9 (45%)				7 (35%)	ns
Headache	3	2	0	5	3	0	0	3	3	1	0	4	ns
Asthenia	2	3	0	5	2	0	0	2	1	3	0	4	ns
Fever/chills	1	0	0	1	0	0	0	0	1	1	0	2	ns
Myalgia	2	0	0	2	4	0	0	4	0	3	0	3	ns
Arthralgia	0	0	0	0	0	1	0	1	0	0	0	0	ns
Dysesthesia/paresthesia	2	0	0	2	0	0	0	0	0	0	0	0	ns
Nausea	0	0	0	0	0	0	0	0	1	0	0	1	ns
Flu-like illness	0	0	0	0	0	0	0	0	0	0	0	0	ns

Subjects used diary cards for 5 days after vaccination to report daily local reactions (erythema, pruritus, pain, induration, swelling, local dysesthesia, and eczema), systemic signs or symptoms (headache, asthenia, fever, chills, myalgia, arthralgia, dysesthesia, paresthesia, and nausea), influenza-like illness (defined as the simultaneous occurrence of fever, chills, myalgia, asthenia, and rhinitis), and any medications. Numbers of local and systemic reactions reported from day 0 to day 5 after vaccination. Statistical analysis was performed with a Fisher's exact test. Statistical significance was set at $p<0.05$ for global comparisons. To take multiple comparisons into account, a Bonferroni correction was performed to compare the occurrence of erythema, pain, induration, and swelling between the three groups. Statistical significance was set at $p<0.0125$ for these comparisons, (ns: no statistical significance). [a] flexural eczema. One participant with a history of seasonal recurrent eczema had severe bilateral flexural eczema one day after t.c. vaccination, which was controlled within three days by treatment with 0.05% betamethasone cream.

Supplemental Table 3: Hemagglutination inhibition (HI) antibody titers against influenza

		Transcutaneous route (n=19)	Intradermal route (n=20)	Intramuscular route (n=20)	P value
		Influenza A/H3N2			
Day 0	GMT (95% CI)	54.2 (36.4–80.6)	42.0 (26.3–67.0)	55.7 (32.8–94.7)	0.7432
	Seroprotection, n (%)	14/20 (70.0%)	14/20 (70.0%)	14/20 (70.0%)	1
Day 21	GMT (95% CI)	48.4 (29.8–78.7)	161.8 (102.8–254.7)	232.1 (128.1–420.8)	**0.0006*** **
	Seroprotection, n (%)	14/19 (73.7%)	20/20 (100.0%)	20/20 (100.0%)	**0.0023** **
	Seroconversion, n (%)	1/19 (5.3%)	8/20 (40.0%)	10/20 (50.0%)	**0.0050** **
Month 5	GMT (95% CI)	49.4 (27.3–89.4)	115.3 (80.2–165.7)	167.2 (85.6–326.5)	**0.0162***
	Seroprotection, n (%)	14/19 (73.7%)	20/20 (100.0%)	15/19 (78.9%)	**0.0394***
	Seroconversion, n (%)	1/19 (5.3%)	6/20 30.0%)	7/19 (36.8%)	0.0507
		Influenza A/H1N1			
Day 0	GMT (95% CI)	12.0 (4.9–29.1)	26.7 (13.7–52.1)	13.8 (6.5–29.0)	0.1369
	Seroprotection, n (%)	6/20 (30.0%)	11/20 (55.0%)	7/20 (35.0%)	0.3381
Day 21	GMT (95% CI)	11.8 (4.7–29.4)	85.0 (42.6–169.7)	92.0 (39.1–216.3)	**0.0010*** **
	Seroprotection, n (%)	6/19 (31.6%)	16/20 (80.0%)	16/20 (80.0%)	**0.0020** **
	Seroconversion, n (%)	1/19 (5.3%)	7/20 (30.0%)	10/20 (50.0%)	**0.007** **
Month 5	GMT (95% CI)	18.3 (7.7–43.6)	45.1 (3.2–18.1)	68.2 (33.9–137.4)	**0.0156***
	Seroprotection, n (%)	9/19 (47.4%)	15/20 (75.0%)	15/19 (78.9%)	0.1014
	Seroconversion, n (%)	2/19 (10.5%)	6/20 (25.0%)	9/19 (47.4%)	**0.0424***
		Influenza B			
Day 0	GMT (95% CI)	1.8 (1.0–3.2)	1.6 (1.0–2.5)	4.1 (1.8–9.2)	0.0756
	Seroprotection, n	1/20 (5.0%)	0/20 (0%)	3/20 (15.0%)	0,3103
Day 21	GMT (95% CI)	2.1 (1.1–3.8)	13.4 (5.2–34.7)	32.6 (16.9–62.8)	**<0.0001*** **
	Seroprotection, n (%)	1/19 (5.3%)	7/20 (35.0%)	10/20 (50.0%)	**0.0070** **
	Seroconversion, n (%)	0/19 (0%)	7/20 (35.0%)	6/20 (30.0%)	**0.0190***
Month 5	GMT (95% CI)	2.7 (1.3–5.5)	7.6 (3.2–18.1)	16.8 (7.2–39.2)	**0.0089** **
	Seroprotection, n (%)	1/19 (5.3%)	5/20 (25.0%)	9/19 (47.4%)	**0.0106***
	Seroconversion, n (%)	0/19 (0%)	5/20 (25.0%)	5/19 (26.3%)	**0.0420***

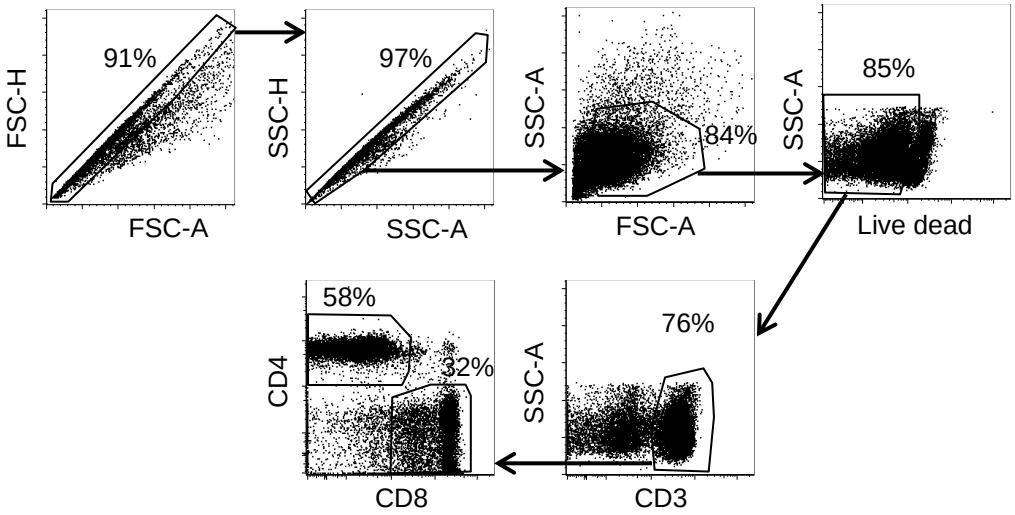
Geometric mean titers (GMT) of hemagglutination inhibition (HI) antibodies and 95% confidence intervals (CIs) on day (D) 0, D21, and month (M) 5 are shown for each vaccination group: transcutaneous (t.c.; n=20 at D0, n=19 at D21 and M5), intradermal (i.d.; n=20), and intramuscular (i.m.; n=20 at D0 and D21, n=19 at M5). Seroprotection rates (i.e., numbers of individuals with HI titers ≥40) and seroconversion rates (i.e., numbers of individuals with HI titers <10 at D0 and HI titers ≥40 after vaccination or with HI titers ≥10 at D0 and ≥4-fold increase in HI titers after vaccination) are also indicated. Kruskal-Wallis tests and Fisher's exact tests were performed to compare the characteristics of the three groups (* P-value<0.05; ** P-value<0.01; *** P-value<0.001).

Supplemental Table 4: Microneutralizing (MN) antibody titers against influenza viral strains

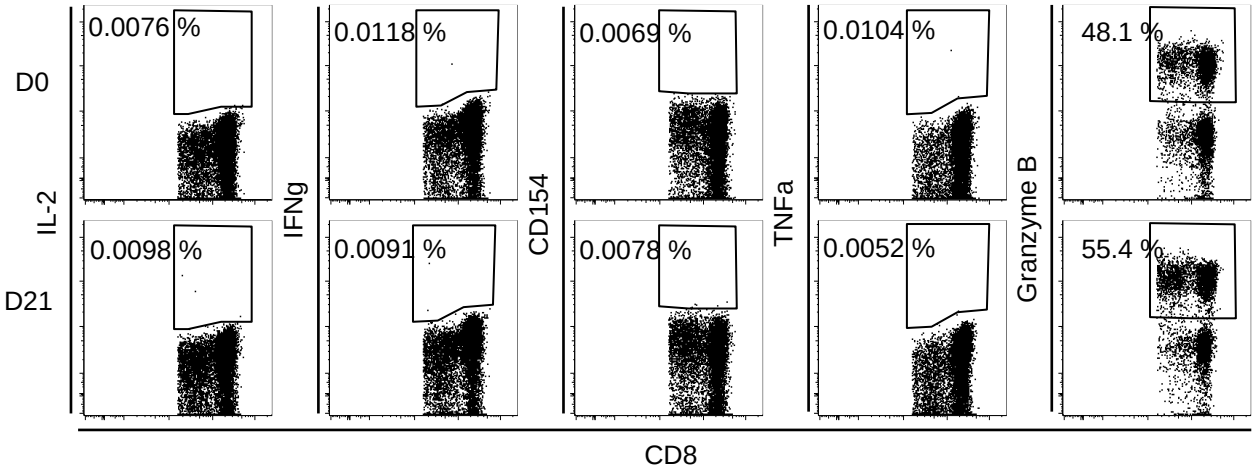
	Transcutaneous route (n=19)	**Intradermal route (n=20)**	**Intramuscular route (n=20)**	**p-value**
		Influenza A/H3N2		
Day 0	41.5 (25.7–66.8)	37.6 (25.6–55.4)	52.8 (32.1–86.9)	0.5891
Day 21	35.4 (22.6–55.5)	232.8 (135.7–399.5)	366.4 (219.1–612.5)	**<0.0001******
Month 5	35.8 (21.9–58.5)	124.5 (76.8–202.0)	190.3 (119.3–303.4)	**<0.0001******
		Influenza A/H1N1		
Day 0	80.2 (28.5–225.8)	127.7 (60.3–270.5)	80.6 (36.9–176.1)	0.4395
Day 21	79.2 (28.7–218.2)	870.7 (394.4–1922)	768.2 (284.9–2072)	**0.0009*****
Month 5	130.9 (51.1–335.6)	449.5 (211.1–957.2)	605 (242.5–1510)	**0.0324***
		Influenza B		
Day 0	41.1 (23.9–70.7)	31.7 (21.8–46.1)	41.5 (25.3–67.8)	0.6698
Day 21	45.6 (27.1–76.7)	183.1 (96.1–349.1)	173 (83–360.6)	**0.0039****
Month 5	50.2 (31.3–80.5)	128.3 (63.9–257.6)	156.2 (83.9–290.6)	**0.0155***

Geometric mean titers GMT (95% CI) of microneutralizing antibodies and 95% confidence intervals (CIs) on day (D) 0, D21, and month (M) 5 are shown for each vaccination group: transcutaneous (n=20 at D0, n=19 at D21, and M5), intradermal (n=20) and intramuscular (n=20 at D0 and D21, n=19 at M5). Kruskal-Wallis tests and Fisher's exact tests were performed to compare the characteristics of the three groups (* P<0.05; ** P<0.01; *** P<0.001; **** P-value<0.0001).

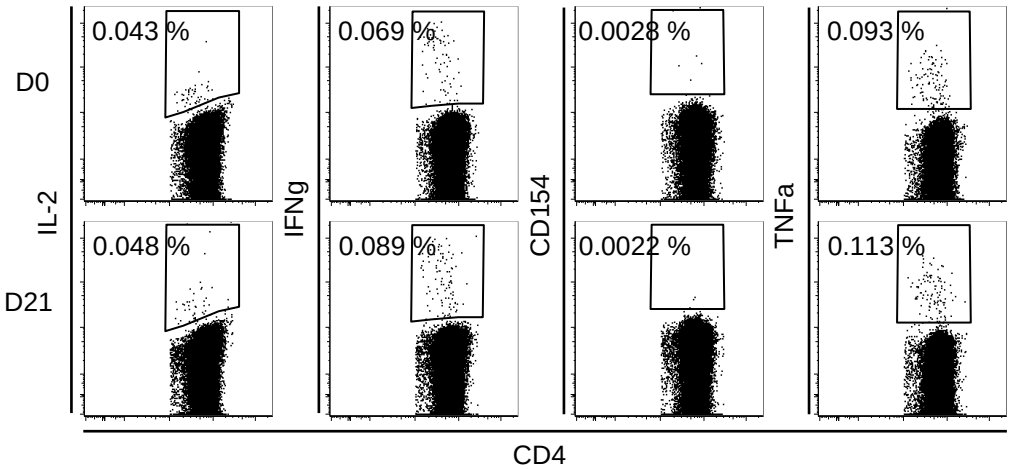
Supplemental Figure 1: Representative gating strategy for identification of IL-2, IFN-γ, TNF-α and Granzyme B (GRZ) on TIV-stimulated CD8 and CD4 T cells at baseline (D0) and D21 post-vaccination. Each gate represents percentage of mother gate.



TIV-stimulated CD8 T cells



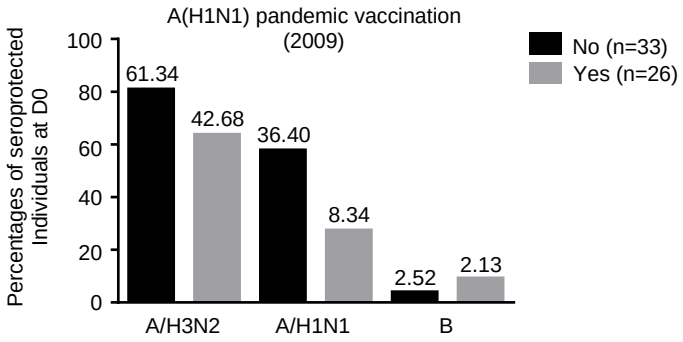
TIV-stimulated CD4 T cells



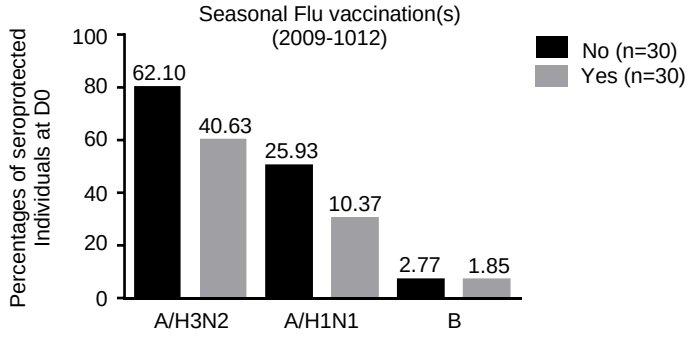
Supplemental Figure 2: Influenza-specific humoral responses at baseline (D0) in individuals who previously received or did not receive at least A/H1N1 pandemic vaccination (2009) or/and previous seasonal TIV vaccine.

Percentages of seroprotected individuals at D0 (i.e., HI titers ≥40) against influenza A/H3N2, A/H1N1, and B viruses included in TIV 2012-2013. HI antibody titers were measured at baseline in individuals who previously either received (Yes) or did not receive (No) A/H1N1 pandemic vaccination (2009) **A**), or previous seasonal TIV immunizations **B**). The number of subjects in each group is indicated. Yes= previous vaccination, No= no influenza vaccination before study enrolment.

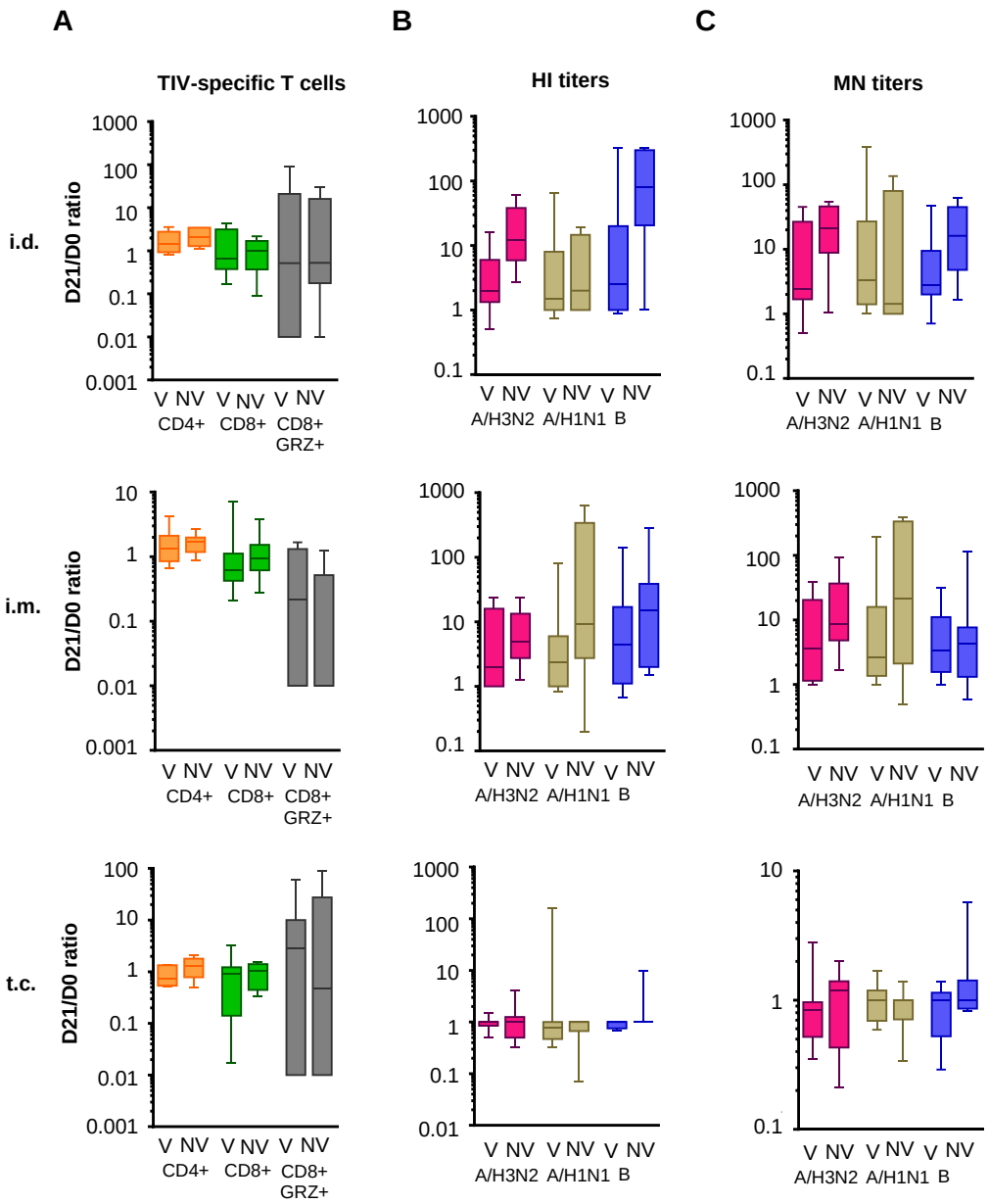
A



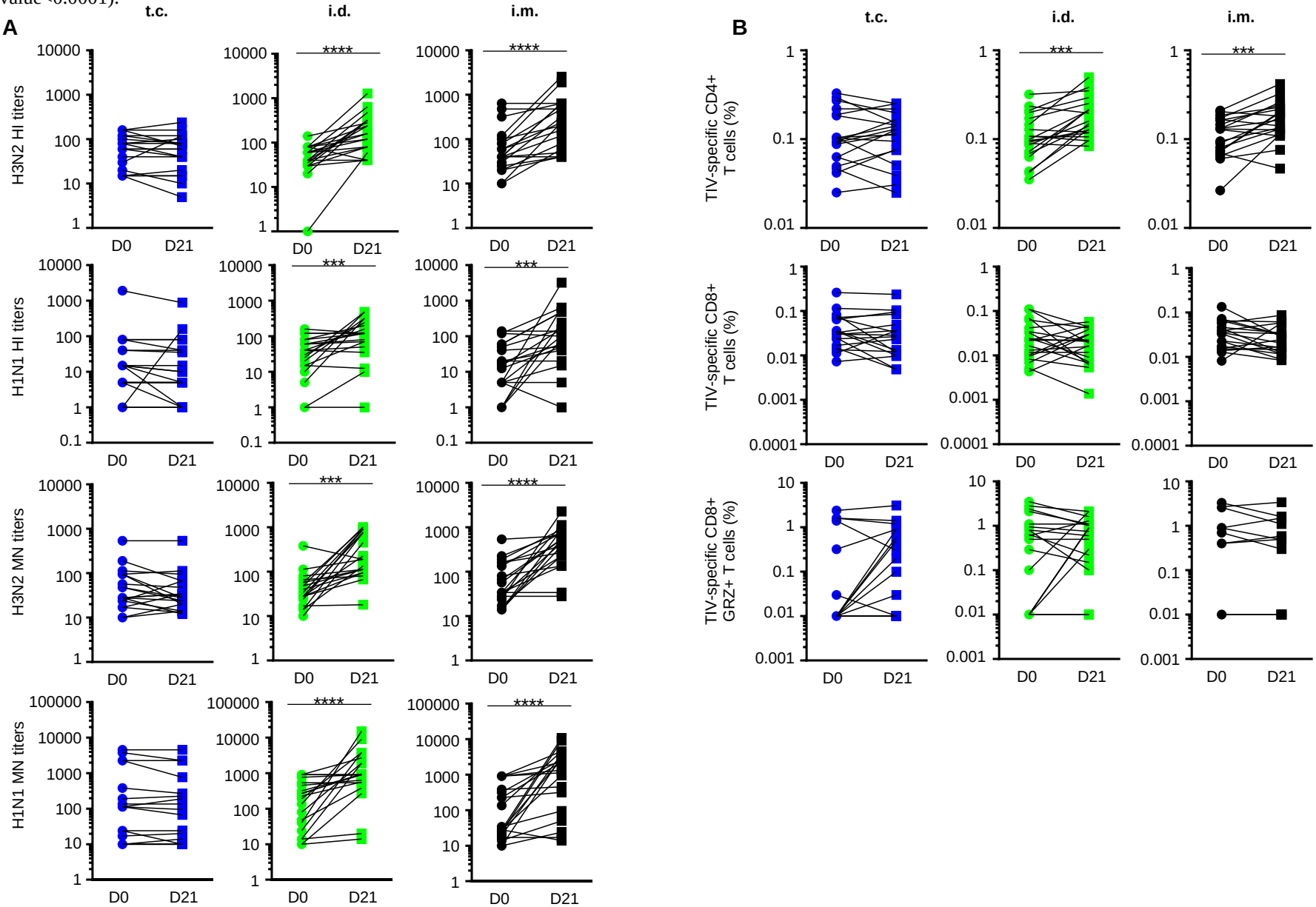
B



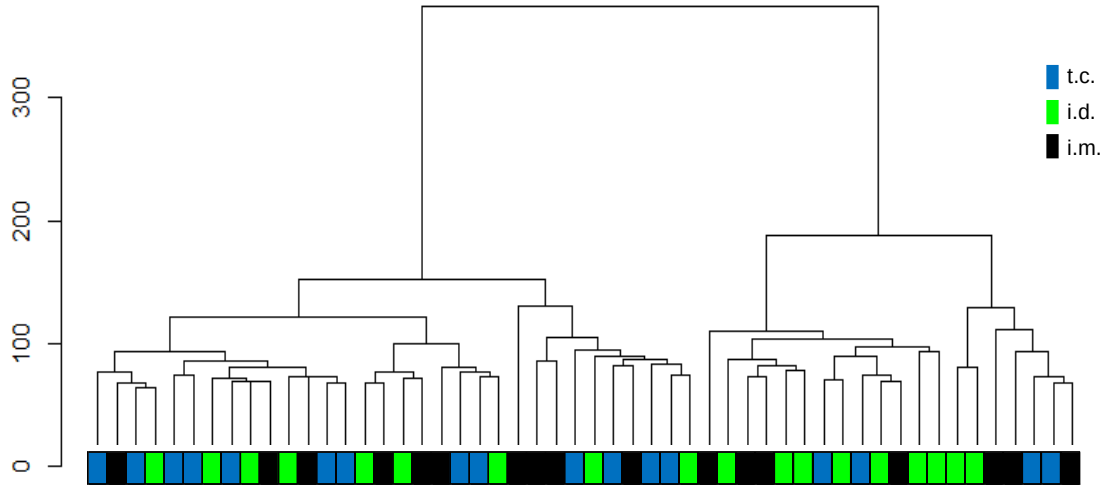
Supplemental Figure 3: TIV-specific cellular immune responses (D21/D0) in individuals who previously received or did not receive at least A/H1N1 pandemic vaccination (2009) or/and previous seasonal TIV vaccine (2009-2012). Box-and-whisker plot of D21/D0 ratios for the TIV-specific immune responses (from the bottom up: the minimum, 25th percentile Q1, median, 75th percentile Q3 and maximum values): cytokine-producing CD4+ and CD8+ T cells and CD8+ GRZ+ T cells (**A**) and HI (**B**) and MN (**C**) antibodies titers against the three A/H3N2, A/H1N1 and B strains for humoral immune responses. The Mann-Whitney *t*-test compared previously vaccinated (V) (i.d. n=15; i.m. n=10; t.c. n=8) to non-previously vaccinated (NV) (i.d. n=5; i.m. n=10; t.c. n=11). No significant result was observed.



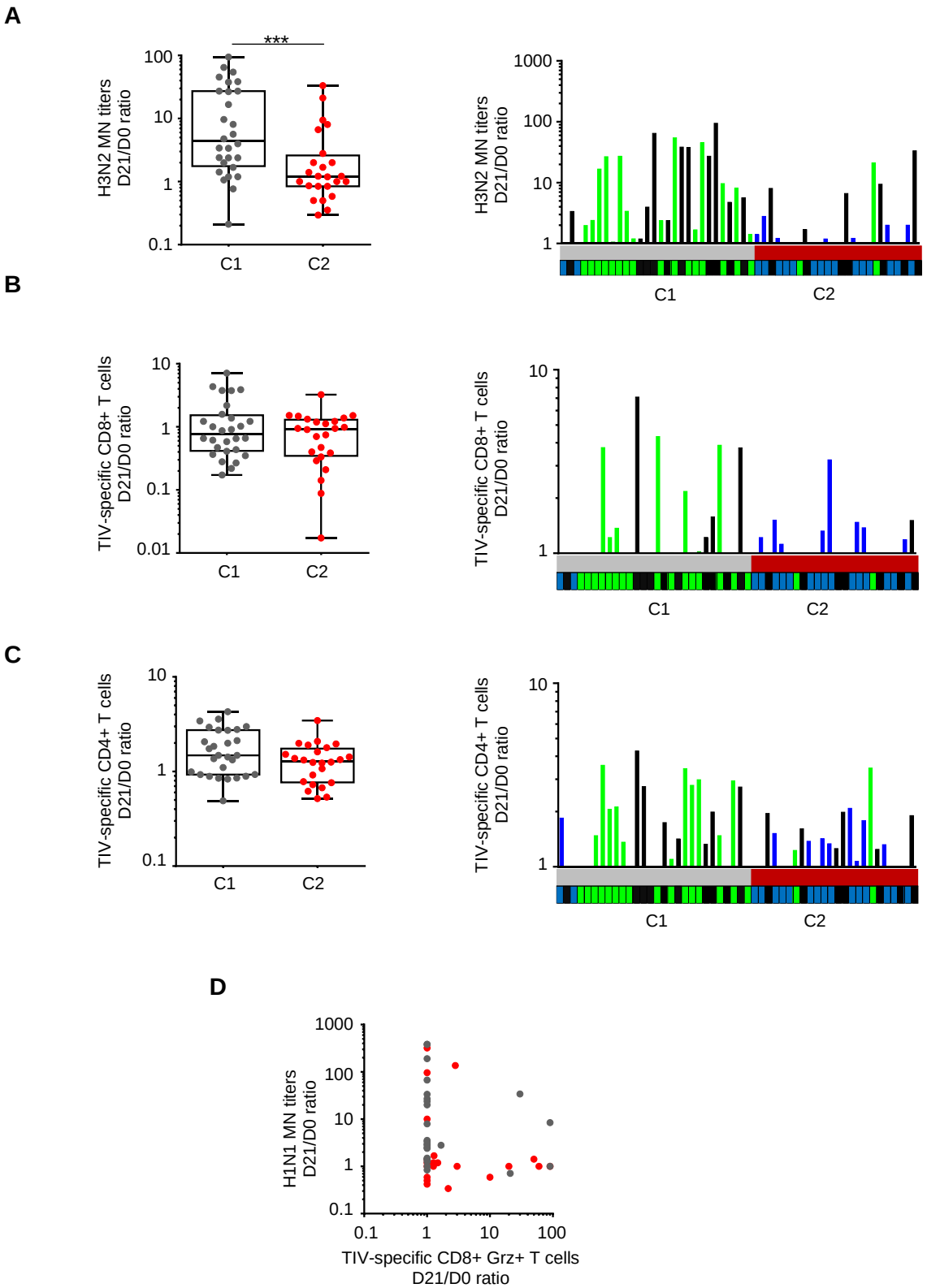
Supplemental Figure 4: TIV specific immune responses at D0 and D21 following t.c., i.d. and i.m. vaccination. Adaptive immune responses before (D0) and after vaccination (D21) for each administration route t.c. (blue, n=19), i.d. (green, n=20) and i.m. (black, n=20) : influenza virus-specific HI and MN antibodies (**A**) and TIV-specific CD4+ and CD8+ cytokines secreting T cells and CD8+GRZ+ T cells (**B**). The Mann-Whitney t-test compared D0 and D21 levels (*** P-value<0.001; **** P-value<0.0001).



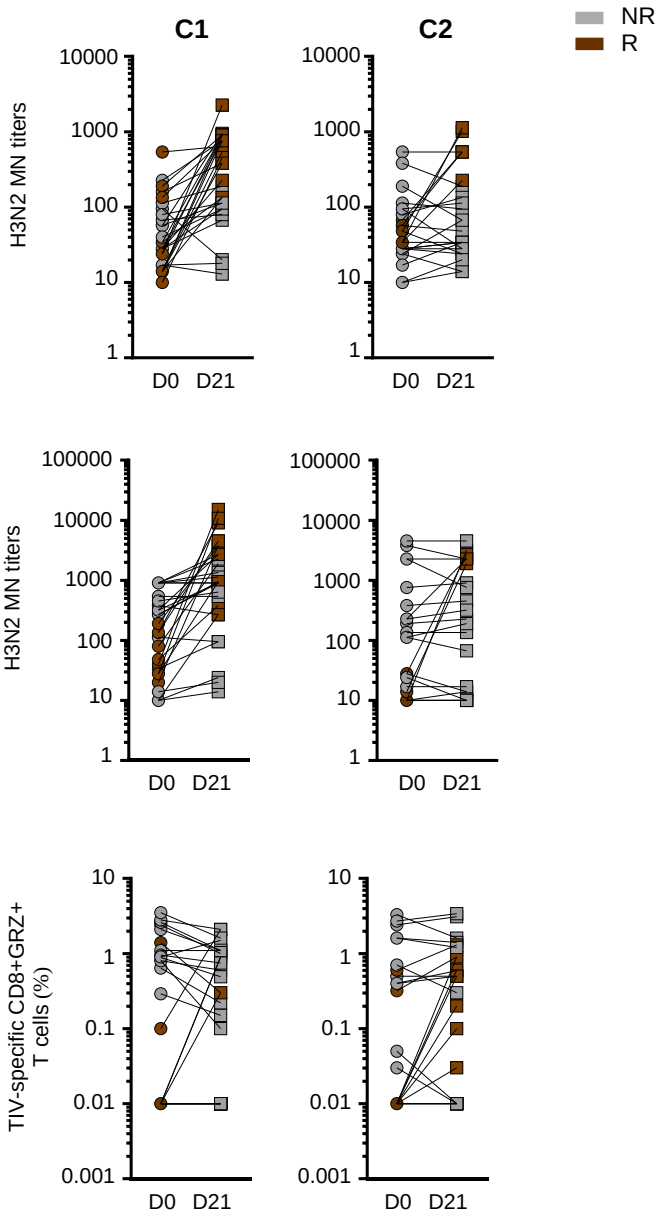
Supplemental Figure 5: Samples dendrogram according to the three administration routes based on genes expression at baseline (D0). Hierarchical clustering based on the expression profile of all identified 47323 genes at baseline (D0) according to the three administration routes (N=52). No gene was found significantly differentially expressed between the three arms at D0 (corrected p-value ≤ 0.1).



Supplemental Figure 6: Immunological responses (D21/D0) between individuals from C1 and C2 clusters. Box-and-whiskers plots (left panels; from the bottom up: the minimum, 25th percentile Q1, median, 75th percentile Q3 and maximum values) with min to max show all sample points (y-axis of graph in log 10 scale). They represent the D21/D0 ratio of the **A**) H3N2 MN titers from the C1 and C2 subjects (C1 n=28: t.c. n=2, i.d. n=16, i.m. n=10 and C2 n=24: t.c. n=15, i.d. n=2, i.m. n=7), the same for **B**) cytokine secreting TIV-specific CD8+ T cells and **C**) TIV-specific CD4+ T cells with the respective histograms of the immune response intensities (right panel). **D**) Scatterplot of H1N1-specific MN antibody titers and TIV-specific CD8+GRZ+ T cells (D21/D0 ratios) highlighting C1 (gray) and C2 (red) individuals. The Mann-Whitney t-test compared C1 and C2 clusters (*** P-value<0.001).



Supplemental Figure 7: Immunological assays at pre-vaccination (D0) and D21 post-vaccination according to samples clusters C1 and C2 based on the 496 genes expression profile. Titers of H3N2-, H1N1-specific microneutralizing antibodies and TIV-specific CD8+GRZ+ T cells at baseline (D0) and 21 days post-vaccination (D21) according to C1 (left) and C2 (right) clusters (C1 n=28 and C2 n=24). Grey and brown points correspond to non-responders and responders, respectively (H3N2MN: C1 R n=14, C2 R n=5 ; H1N1MN: C1 R n=11, C2 R n=4 ; TIV-specific CD8+GRZ+ T cells: C1 R n=4, C2 R n=8).

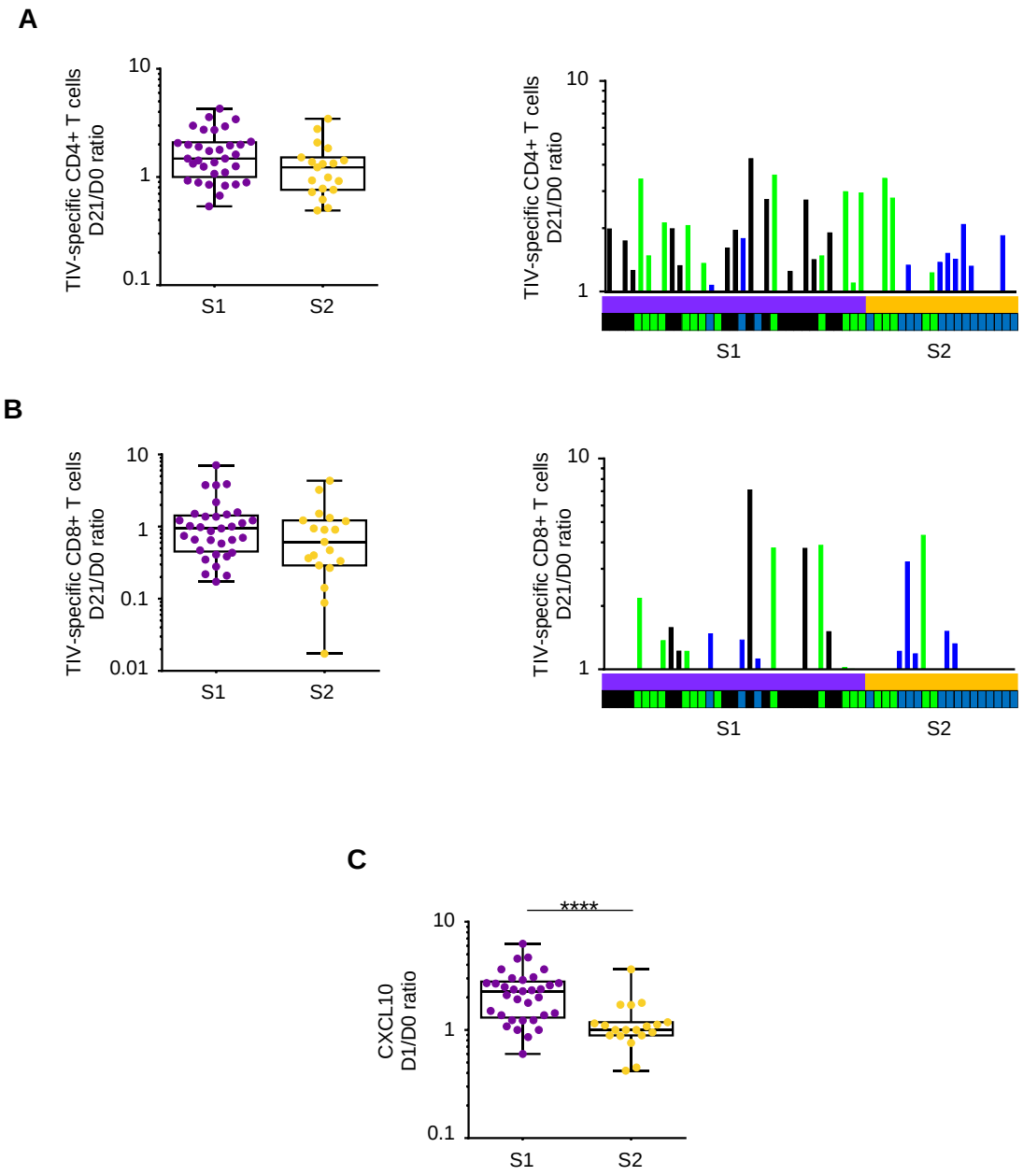


Supplemental Table 5: List of top genes correlated with H1N1- or H3N2-specific MN antibody titers and with TIV-specific CD8+GRZ+ T-cell responses among 496 genes.

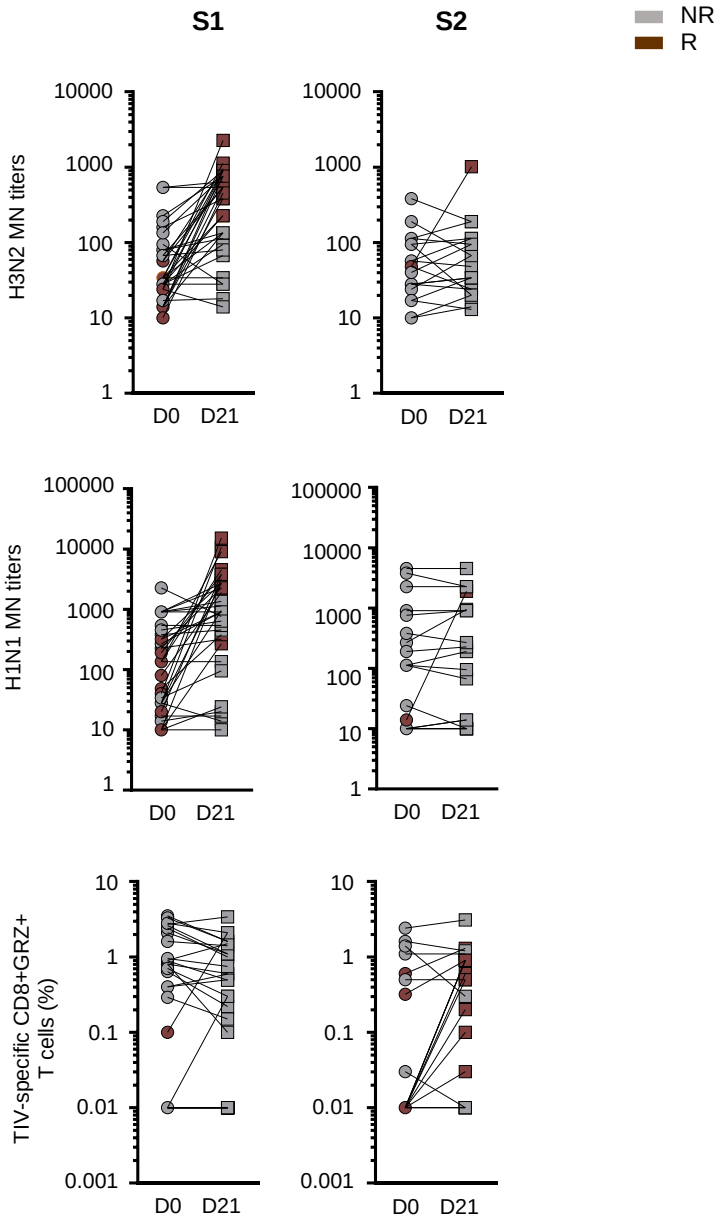
Genes	H1N1 MNAb		H3N2 MNAb		CD8+Grz+ T cells	
	P-value	***r***	***P-value***	***r***	***P-value***	***r***
CKS1B	9.8E-03	0.36	1.31E-02	0.34	-	-
C2	5.02E-06	0.59	2.66E-04	0.48	-	-
CXCR2P1	5.89E-04	0.46	2.3E-02	0.32	-	-
CXCR4	-	-	-	-	3.4E-02	-0.29
TMEM8B	4.1E-02	-0.28	1.7E-02	-0.33	-	-
PRKAA1	2.69E-07	-0.64	1.16E-04	-0.51	-	-
PVRL1	-	-	-	-	4.1E-02	0.28
SARM1	-	-	-	-	3.3E-03	0.40
MAP2K5	-	-	-	-	3.4E-02	0.29

Spearman correlation test (P<0.05).

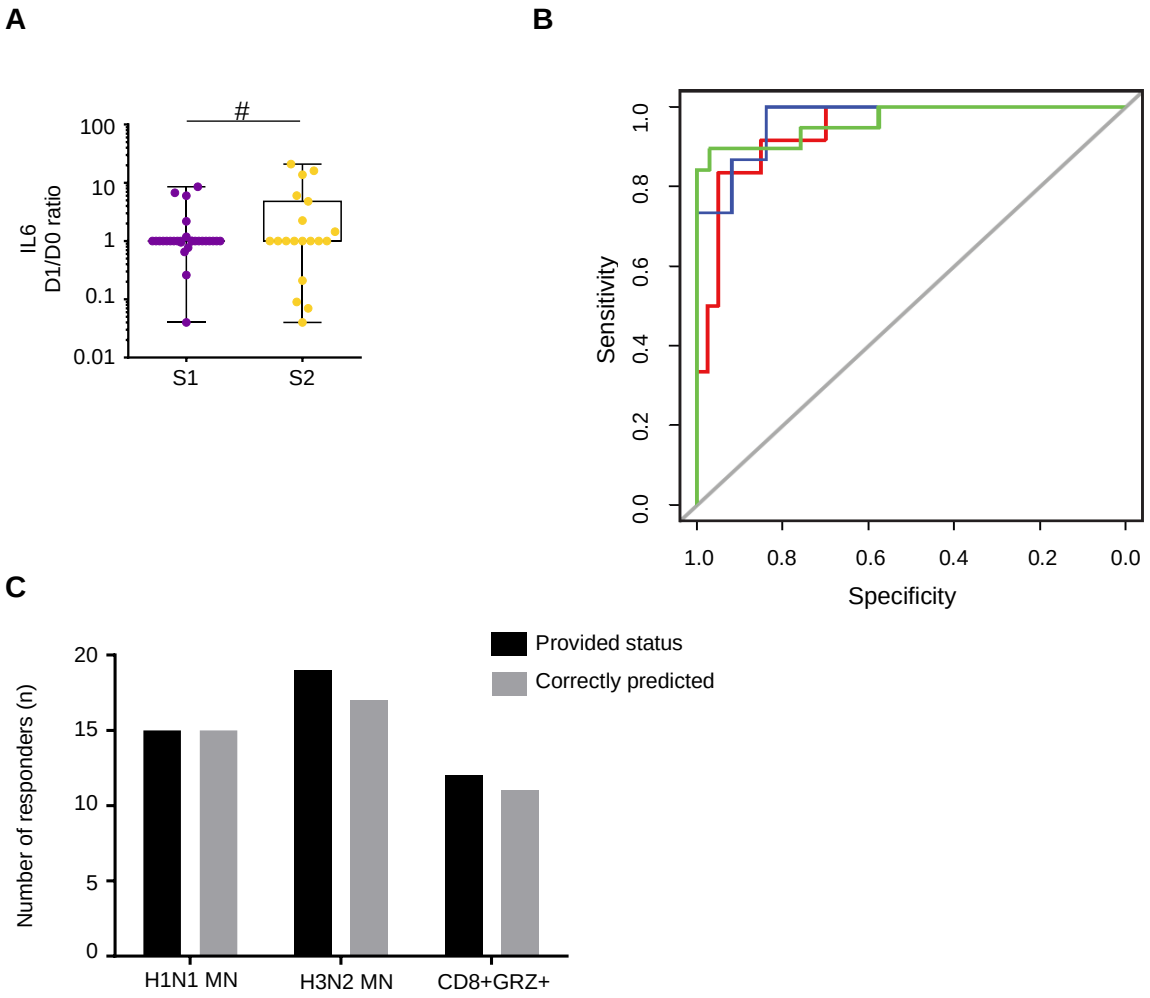
Supplemental Figure 8: Immunological outcomes comparison between individuals from S1 and S2 clusters. A and **B**) Box-and-whiskers plots (left panels; from the bottom up: the minimum, 25th percentile Q1, median, 75th percentile Q3 and maximum values) with min to max show all sample points (y-axis of graph in log 10 scale). They represent the D21/D0 ratio of the TIV-specific cytokine secreting CD4+ T cells and CD8+ T cells from the S1 (purple) and S2 (yellow) clusters (S1 n=33: t.c. n=3, i.d. n=13, i.m. n=17 and S2 n=19: t.c. n=14, i.d. n=5) with the respective histograms of the immune responses (right panel). **C**) Box-and-whiskers plot of the CXCL10 concentration ratios (D1/D0) from the S1 and S2 samples. The Mann-Whitney t-test compared S1 and S2 clusters (**** P-value<0.0001).



Supplemental Figure 9: Immunological assays at pre-vaccination (D0) and D21 post-vaccination according to samples clusters S1 and S2 based on the 9 genes expression profile. Titers of H3N2-, H1N1- specific MN antibodies (upper and middle graphs) and TIV-specific CD8+GRZ+ T cells (lower graphs) at baseline (D0) and 21 days post-vaccination (D21) according to S1 (left) and S2 (right) clusters (S1 n=33 and S2 n=19). Grey and brown points correspond to non-responders and responders respectively (H3N2MN: S1 R n=18, S2 R n=1 ; H1N1MN: S1 R n=14, S2 R n=1 ; TIV-specific CD8+GRZ+ T cells: S1 R n=2, S2 R n=10).



Supplemental Figure 10: CXCL10, IL-6 serum levels and the 9 genes signature significantly explain both three immune responses: H1N1 and H3N2-specific MN antibody titers and CD8+GRZ+ T cells. A) Box-and-whiskers plot with the min to max (from the bottom up: the minimum, 25th percentile Q1, median, 75th percentile Q3 and maximum values) represents the D1/D0 ratio for serum concentrations of IL-6 from the S1 (purple) and S2 (yellow) clusters (S1 n=33: t.c. n=3, i.d. n=13, i.m. n=17 and S2 n=19: t.c. n=14, i.d. n=5). The y-axis of the graph is in log 10 scale. The Chi2 test for qualitative variables (# P-value<0.05). **B**) ROC curves showing the specificity and sensitivity of the logistic regression models *i.e.* the proportion of correctly predicted responders and nonresponders (N=52), respectively. The curves correspond to the D21/D0 ratio of immune responses: H1N1-specific MN antibody titers (blue; area under the curve (AUC=0.9694), H3N2-specific MN antibody titers (green; AUC=0.9633) and TIV-specific CD8+GRZ+ T cells (red; AUC=0.9417). The 9 gene expression profiles, the IL-6 and CXCL10 serum levels significantly explain each of these variables. **C)** The histogram represents the number of responders individuals for each immune response: H1N1/H3N2 MN antibodies (D21/D0 ratio ≥ 4) and TIV-specific CD8+GRZ+ T lymphocytes (D21/D0 ratio ≥ 2), in regard to provided status (Black) and correctly predicted status (grey) based on the early 9 genes expression and CXCL10 and IL-6 serum levels (D1/D0). The percent individuals predicted as responders for H1N1- and H3N2-specific MN antibody and TIV-specific CD8+GRZ+ T cells responses is 100%, 89.47% and 91.66%, respectively.



Supplemental Materials and Methods

Hemagglutination inhibition and microneutralization assay

At D0, D21, and M5, serum antibodies against the three influenza viral strains contained in the 2012–2013 influenza vaccine were measured with a microtiter hemagglutination inhibition (HI) assay. Briefly, after treatment with receptor-destroying enzyme, serial 2-fold dilutions of serum (starting at 1:10) were tested against 4 hemagglutinin units of antigen in human O+ Rh− red blood cells. The HI titers were defined as the reciprocal of the highest serum dilution that completely inhibited hemagglutination. Seroprotection was defined as an HI titer ≥40. Seroconversion was defined as either an HI titer ≤10 at D0 and ≥40 after vaccination or an HI titer >10 at D0 with a ≥4-fold increase after vaccination.

Neutralizing Ab titers were measured by microneutralization (MN) assays. Serum samples were first heat-inactivated at 56°C for 30 minutes. Serial 2-fold dilutions of serum (from 1:10) were added separately to 10^3 TCID50 of each of the three vaccine strains and incubated at 37°C for 2 hours before transfer onto 96-well microtiter plates containing confluent MDCK (Madin-Darby canine kidney) cells. The neutralization titer was expressed as the reciprocal of the highest serum dilution that blocked virus infection after 3 days of culture.

We defined responders as those with MN or HI titers with an increase >4-fold in antibody titers at D21 compared to baseline at D0.

Intracellular cytokine assay

Peripheral blood mononuclear cells (PBMCs) were isolated by density gradient separation from heparinized whole blood. Cells were processed within 4 hours of collection and stored at 1×10^7 cells/mL in freezing medium (10% DMSO (Sigma-Aldrich), 90% fetal bovine serum) at -80°C before storage in vapor phase liquid nitrogen until analysis. Frozen peripheral blood lymphocytes were used for analysis of vaccine-specific T cells at D0 and D21. Cells were stimulated at 37°C for 16 hours with or without Vaxigrip® at 100 ng/mL of hemagglutinin. Brefeldin-A and monensin (Sigma-Aldrich) were added for the last 14 hours of incubation. Cells were washed and stained in PBS containing 2% fetal calf serum at 4°C with Live/Dead Fixable Aqua (Molecular Probes), CD4 (OKT4 clone; Biolegend), CD3 (SK7

clone; BD Biosciences), CD8 (RPA-T8 clone; BD Biosciences), and CD154-PE (TRAP1 clone; BD Biosciences) mAbs. The Cytofix/Cytoperm kit (BD-Biosciences) was used before staining with interleukin-2 (IL-2; N7.48 A clone; Miltenyi), interferon-gamma (IFN-γ; B27 clone; BD Biosciences), tumor necrosis factor-alpha (TNF-α; MAb11 clone; BD Biosciences), and Granzyme B (GRZ; GB11 clone; BD Biosciences) mAbs. Background cytokine responses detected in unstimulated negative controls were subtracted from those detected in vaccine-stimulated samples. The percentage of vaccine-specific CD4+ or CD8+ T cells was determined as the sum of the 15 possible combinations of cells expressing at least one of the IL-2, IFN-γ, TNF-α, or CD154 markers by Boolean combination gating with FlowJo software (FlowJo, LLC). We defined responders with D21/D0 ratio ≥ 2 for TIV-specific cytokine-producing CD8+ T cells, and TIV-specific GRZ+ CD8+ T lymphocytes. Flow cytometry was performed with an LSRII flow cytometer (BD Biosciences Immunocytometry Systems) with at least one million live events.

Cytometric bead arrays

Concentrations of CXCL10 and IL-6 were measured in the serum samples collected at D1 and D0 (n=59) by cytometric bead arrays (BD Biosciences) and flow cytometry, according to the manufacturer's protocol. FCAP Array v3.0 software (BD Biosciences) was used for the analysis. Minimum levels of detection were 10 pg/mL for CXCL10 and 274 fg/mL for IL-6 (Enhanced sensitivity flex sets, BD).

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-4
	2b	Specific objectives or hypotheses	3-4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	15-16
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Not applicable
Participants	4a	Eligibility criteria for participants	15-16
	4b	Settings and locations where the data were collected	15-16
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	15-16
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	15-16
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Not applicable
Sample size	7a	How sample size was determined	15
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Not applicable
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	15
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	15
Allocation concealmen	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	15

t mechanism			
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	15
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Not applicable
	11b	If relevant, description of the similarity of interventions	15
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	16-17
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	16-17
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	5 + Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	5 + Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5
	14b	Why the trial ended or was stopped	Not applicable
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Supplemental table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	5-6 + Figure 1 + Supplemental Tables
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	5-6
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	7-9
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Not applicable
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of	10

		analyses	
Generalisability	**21**	**Generalisability (external validity, applicability) of the trial findings**	**11**
Interpretation	**22**	**Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence**	**11-13**
Other information			
Registration	**23**	**Registration number and name of trial registry**	**2**
Protocol	**24**	**Where the full trial protocol can be accessed, if available**	**Submitted**
Funding	**25**	**Sources of funding and other support (such as supply of drugs), role of funders**	**2**

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.