Figure 1.

(A)



(B)



Table 1.

	All	SHORT 2 - 5 Weeks	LONG 6 - 14 Weeks
Dosing Interval			
Median Days	70	24	70
Median Weeks	10.00	3.43	10.00
IQR (Days)	62-75	21-26	63-77
Range (Days)	14-99	14-35	44-99
N	503	75	428
Female, N (%)	376 (75%)	46 (61%)	330 (77%)
Male, N (%)	127 (25%)	29 (39%)	98 (23%)
Mean Age	42.61	44.68	42.25
Age in years, Median (IQR)	43 (33-52)	45 (37-54)	43 (32-51)
Age Range	22-71	22-71	22-71
Infection Status			
Naïve, N (%)	280 (56%)	51 (68%)	229 (54%)
Previous SARS-CoV-2, N (%)	223 (44%)	24 (32%)	199 (46%)
Ethnicity (Self Reported)			
White <i>,</i> N (%)	337 (67%)	44 (59%)	293 (68%)
Asian, N (%)	37 (7%)	3 (4%)	34 (8%)
Black, N (%)	3 (1%)	0 (0%)	3 (1%)
Other, N (%)	15 (3%)	4 (5%)	11 (3%)
Unreported, N (%)	111 (22%)	24 (32%)	87 (20%)

Generalized linear models (GLM) of T cell (IFN_Y) or antibody (IgG) immune responses

	Spike T cell re parti	sponses in naive and previ icipants at dose-2 plus 4 w	Spike A particip	Antibody responses in pants at dose-2 plus 4	n naive I weeks	Spike Antibody responses in previously infected participants at dose-2 plus 4 weeks			
Coeffcient	Estimates	utes Conf. Int (95%) P-Value		Estimates	Conf. Int (95%)	P-Value	Estimates	Conf. Int (95%)	P-Value
Intercept	2.21	1.90 - 2.51	<0.001	5.40	5.18 - 5.63	<0.001	5.50	5.26 - 5.73	<0.001
Age	-0.00	-0.01 - 0.00	0.522	-0.01	-0.010.00	0.020	0.00	-0.00 - 0.00	0.554
Sex (M)	-0.06	-0.21 - 0.08	0.404	-0.10	-0.20 - 0.00	0.060	0.02	-0.09 - 0.13	0.690
Previously infected (Yes)	0.38	0.24 - 0.51	<0.001						
Vaccine dose interval (Long)	-0.19	-0.370.01	0.041	0.20	0.08 - 0.32	0.001	0.01	-0.14 - 0.17	0.886
Observations	374			189			184		
R2	0.086			0.131			0.003		

Linear mixed-effect models (LMER) of T cell (IFN_Y) or antibody (IgG) immune responses

	Spike T cell responses in naive participants			Spike T cell responses in preinfected participants			Spike Antibody responses in naive participants			Spike Antibody responses in preinfected participants		
Coeffcient	Estimates	Conf. Int (95%)	P-Value	Estimates	Conf. Int (95%)	P-Value	Estimates	Conf. Int (95%)	P-Value	Estimates	Conf. Int (95%)	P-Value
Intercept	1.47	0.95 - 1.98	<0.001	1.92	1.26 - 2.59	<0.001	4.84	4.42 - 5.26	<0.001	5.77	5.41 - 6.12	<0.001
Age	-0.00	-0.02 - 0.01	0.705	0.01	-0.01 - 0.02	0.480	-0.01	-0.02 - 0.00	0.090	-0.00	-0.01 - 0.01	0.640
Sex (M)	-0.15	-0.54 - 0.23	0.435	0.42	0.01 - 0.84	0.046	0.09	-0.26 - 0.45	0.608	-0.04	-0.29 - 0.21	0.757
Timepoint (Pre vaccine)	-0.79	-1.080.50	<0.001	-0.88	-1.09 – -0.67	<0.001	-2.79	-2.952.63	<0.001	-1.65	-1.77 – -1.54	<0.001
Timepoint (Dose-1 plus 10 weeks)	0.28	-0.01 - 0.57	0.060	0.08	-0.13 - 0.28	0.466	-0.38	-0.530.22	<0.001	-0.18	-0.290.07	0.002
Timepoint (Dose-2 plus 4 weeks)	0.85	0.56 - 1.13	<0.001	0.31	0.10 - 0.51	0.003	0.97	0.81 – 1.12	<0.001	-0.02	-0.13 - 0.10	0.793
Random Effects									1			
σ2	0.28			0.14			0.09			0.05		
τ_{00}	0.06 PubII	D		0.12 PubID			0.09 PubID		1	0.04 PubID		
ICC	0.18			0.46			0.49		1	0.43		
Ν	26 _{PubID}			26 _{PubID}			29 _{PubID}			29_{PubID}		
Observations	103			104			116		l	116		
Marginal R ² / Conditional R ²	0.506 / 0.	593		0.462 / 0.71	0		0.914 / 0.9	56		0.848 / 0.913	3	

Figure 2.

(A) Neutralizing antibody titers – Long interval



(B) Antibody responses : IgG – Long interval



(C) T-cell responses : IFN-y – Long interval



Figure 3.

(A) Neutralizing antibody titers Short versus Long interval

(B) Antibody responses : ACE2 inhibition Short versus Long interval



(C) Antibody responses : IgG – Short versus Long interval







Figure 4

(A) Proportion of response in CD4+ cells



(B) Cytokine expression in spike-specific CD4⁺ cells



(C) Cytokine expression in spike-specific CD8⁺ cells



Figure 5.



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Supplementary Figure 1.



Overview of assays performed and number of samples. MSD = Mesoscale Discovery (MSD) binding assays

SL ementary Figure 2.

(all timepoints and dosing intervals, naive only)

A. Relationship between IgG response to spike (MSD) and nAB response to Victoria (all timepoints and dosing intervals, naïve only

All Altheipreiptsintsaive



tionship between IgG to spike (MSD) and NAb to Victoria V2 + 4 weekគe(និព៌ថកនៃគឺរ**្យទាទះលិខារាល្លាចាំទេះទាវាទូចាំទះទាវិនិ**ទទិទី/ទទួ**គ**សៀMSD) and nAB response to Victoria at dose-2 plus 4 weeks (short and long dosing intervals, naïve only)



1 plus 4 weeks, naïve only

1-dose_doseveeks, naive



Relationship between NAb to Victoria and ELISpot to spike for samples at V2 + 4 weeks (all dosing intervals)

G. Relationship between Nab to Victoria and T cell responses to Spike at dose-2 plus 4 weeks (short and long dosing intervals)

2-dose +24 choeseks, 4 naiveks, naive



FRNT50 REENNIGERARSeripmocalusterum dilution

Relationship between IgG to spike (MSD) and NAb to Victoria (all timepoints and dosing intervals, naive only)

B. Relationship between IgG response to Receptor binding domain (MSD) and nAB response to Victoria (all timepoints and dosing intervals, naïve only

All Altheip coip traints invaive



Relationship between IgG to Receptor binding domain (MSD) and MARIA Winshrip wet We en Agreekspichter & Receptors in a dintervalisa in gives on What nAB response to Victoria at dose-2 plus 4 weeks (short and long dosing intervals, naïve only)



E. Relationship between Nab to Victoria and T cell responses to Spike at dose- F. Relationship between Nab to Victoria and T cell responses to Spike at dose-1 plus 10 weeks, naïve only

1-dose-dose weeks naive



Relationship between NAb to Victoria and ELISpot to spike for samples at V2 + 13 weeks (BNT162b2 short interval)

> H. Relationship between Nab to Victoria and T cell responses to Spike at dose-2 plus 13 weeks (short dosing interval)

2-dose +21-81 overeks, 3 naiveks, naive



Supplementary Figure 3.

(A) Correlation between dosing interval and neutralizing antibodies at 2nd dose plus 4 weeks



Vaccine interval days





Supplementary Figure 3

(A) Correlation between dosing interval in days and neutralizing antibodies to Spike B (early pandemic strain), in naïve participants 4 weeks after the second dose. Spearman's correlation was performed.

(B) Effect of a dosing interval grouped 4 weekly on SARS-CoV-2 S-specific IgG responses in naïve (grey symbols) and pre-infected individuals (red symbols). IgG responses were measured in serum 4weeks after the second dose using multiplexed MSD immunoassays and are shown in Arbitrary Units/ml (AU/ml). Bars represent the median with interquartile range. Unpaired comparisons between the groups were performed using a Mann-Whitney test.

Supplementary Figure 4.



Supplementary Figure 4. MSD sensitivity. Effect of a short or a long vaccine dosing interval on SARS-CoV-2 S-, RBD- and N-specific IgG responses in naïve (grey symbols) and pre-infected individuals (red symbols) after removing participants with IgG N responses above the sensitivity threshold. IgG responses were measured in serum 4 weeks following the second dose using multiplexed MSD immunoassays and are shown in Arbitrary Units/ml (AU/ml). Bars represent the median with interquartile range. Unpaired comparisons between the groups were performed using a Mann-Whitney test. Horizontal dotted lines represent the cut-offs of each assay based on pre-pandemic sera.

Supplementary Figure 5.

(A) Correlation between IgG (MSD) and T cell (ELISpot) response to spike, 4 weeks after 2nd dose, short and long dosing interval, naïve and previously infected







Supplementary Figure 5.

(A) Correlation of IFN-y ELISpot responses to Spike B and anti-spike IgG response , in participants 4 weeks after the second dose in naïve, and previously infected individuals who received either the long or short interval dose. Data points are coloured by ethnic group. Spearman's correlation was performed.

(B) Comparison of of IFN-y ELISpot responses to Spike B, from cryo-preserved PBMCs 4 weeks after second dose in naïve, and previously infected individuals who received the long interval dose, across the 5 centres (BIR: Birmingham, LIV: Liverpool, NEW: Newcastle, OX: Oxford, SHEF: Sheffield) Unpaired comparisons across two groups were performed using the Mann Whitney test. Grey symbols represent naïve individuals, Red symbols represent previously infected individuals.

Supplementary Figure 6.



Supplementary Figure 6. Analysis of polyfunctional Spike specific T cell responses. Simplified Presentation of Incredibly Complex Evaluations (SPICE) analysis of polyfunctional Spike specific T cells. Participants were selected for SPICE analysis based on having at least 50 responding cells, and % cytokine+ cells at least double the background value. (A) 67 participants were suitable for CD4+ T cell analysis and (B) 30 subjects were suitable for CD8+ T cell SPICE analysis. Red pie slices indicate cells making all three functions, yellow indicate cells making two functions and blue one function, in any combination. The arcs indicate the proportion making the individual functions shown. Permutation testing, assessing differences between pie charts between short and long vaccination regimens were performed in both naïve and exposed groups, the difference in T cell function was significant changes in naïve (p = 0.0482) but not exposed (p = ns) subjects. No significant differences were observed in CD8+ cells.

Supplementary Table 1. Generalized linear models (GLM). Table shows three GLM models of T cell (naïve and previously infected individuals), antibody (naïve individuals) and antibody (previously infected individual) responses at 4 weeks after second dose. Variables include age, sex, previous infection, Ethnicity and vaccine dose interval. Variable references are Sex ; F (Female) versus M (Male), Previously infected; Yes versus No, Ethnicity; White versus Black/Asian/Mixed/Other, and Vaccine dose interval; Short versus Long.

	Spike T cell infected par	responses in naive and rticipants at dose-2 plu	Spike An participa	ntibody responses nts at dose-2 plus	in naive 4 weeks	Spike Antibody responses in previously infected participants at dose-2 plus 4 weeks			
Coeffcient	Estimates	Conf. Int (95%)	P-Value	Estimates	Conf. Int (95%)	P-Value	Estimates	Conf. Int (95%)	P-Value
Intercept	2.38	2.03 - 2.73	<0.001	5.39	5.14 - 5.65	<0.001	5.53	5.22 - 5.85	<0.001
Age	-0.01	-0.01 - 0.00	0.060	-0.01	-0.010.00	0.051	0.00	-0.00 - 0.00	0.926
Sex (M)	-0.04	-0.20 - 0.13	0.683	-0.07	-0.19 - 0.05	0.232	0.05	-0.08 - 0.17	0.476
Previously infected (Yes)	0.36	0.19 - 0.52	<0.001						
Ethnicity (Black)	0.18	-0.55 - 0.91	0.623	0.05	-0.63 - 0.72	0.893	0.13	-0.19 - 0.46	0.416
Ethnicity (Asian)	-0.16	-0.42 - 0.09	0.203	0.05	-0.16 - 0.27	0.645	0.10	-0.08 - 0.28	0.258
Ethnicity (Mixed)	-0.16	-0.68 - 0.37	0.560	0.42	-0.25 - 1.10	0.223	-0.63	-1.230.03	0.043
Ethnicity (Other)	-0.05	-0.57 - 0.48	0.867	-0.18	-0.57 - 0.21	0.374	0.16	-0.16 - 0.49	0.326
Vaccine dose interval (Long)	-0.20	-0.42 - 0.01	0.060	0.19	0.05 - 0.32	0.007	-0.01	-0.24 - 0.22	0.908
Observations	277			143			139		

R² 0.085

0.131

0.058