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Supplementary appendix

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SUPPMENTAL APPENDIX

Dynamics of inflammatory responses after SARS-CoV-2 infection by vaccination status: a prospective cohort study

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Supplemental Figure 1. Flow diagram of the study population.

Note: this figure has already been published on https://www.medrxiv.org/content/10.1101/2023.02.13.23285855v1

Analyte	Prevalence of imputed values	Prevalence of outliers
5	(n=2646 person-visits)	(n=2646 person-visits)
IL-1RA	0.1%	2.2%
IL-2RA	0.0%	1.9%
IL-6	0.9%	3.4%
IL-7	0.2%	0.5%
IL-8	0.6%	6.1%
IL-10	7.6%	6.5%
IL-15	0.0%	2.7%
IL-16	0.0%	2.2%
IL-17A	19.8%	12.0%
IL-18	0.4%	7.1%
IL-21	5.3%	2.4%
IL-22	25.6%	16.5%
IL-29/IFN-λ	2.1%	4.0%
IFN-α2a	40.4%	5.4%
IFN-γ	4.3%	8.8%
IP-10	0.4%	3.7%
MCP-1	0.6%	3.4%
MIP-1a	9.0%	7.9%
TNF-α	2.5%	7.6%
VEGF-A	0.6%	2.6%
VCAM-1	1.5%	5.3%

Supplemental Table 1. Prevalence of sample imputed values and outlier values that were excluded.

Note: Missing values were the cytokine levels outside of the assay fit curve range (specific to each plate and analyte) and were imputed. Outliers were the cytokine levels above Q3+1.5×IQR or below Q1-1.5×IQR for each cytokine (specific to each visit and each analyte) and were excluded.

Supplemental Figure 2. The distribution of log_{10} transformed cytokine and chemokine levels at screening by screening vaccination status.



Supplemental Figure 3. The distribution of log_{10} transformed cytokine and chemokine levels at day 14 by day 14 vaccination status.



Supplemental Figure 4. The distribution of log_{10} transformed cytokine and chemokine levels at day 90 by day 90 vaccination status.





Supplemental Figure 5. Day 14 cytokine levels stratified by day 14 vaccination status

Supplemental Figure 6. Differences of the cytokine levels between unvaccinated and partially vaccinated participants.

Note: ratio (95% CI) of geometric mean between the unvaccinated (denominator) and partially vaccinated (numerator) in pg/mL of each cytokine and chemokine are presented.

Each analyte had a separate mixed effect model and all the models were adjusted for age, sex, BMI, hypertension, diabetes, treatment arms, and COVID-19 waves. Treatment arms were not adjusted at screening, since participants were not transfused at screening.

Among the covariates, only BMI have missing data, and the prevalence of missingness was 5%. Available case method was used to exclude missing values.

Assav	Visit	Ratio of geometric mean (95% CI),	Ratio of geometric mean	P value
Assay	TISIC	partially vaccinated / unvaccinated	(95% CI)	1 value
IL-1RA	Screening	— —	0.81 (0.71, 0.93)	0.0036
	Day 14	—•— i	0.84 (0.75, 0.95)	0.0062
	Day 90		1.04 (0.93, 1.15)	0.48
IL-2RA	Screening	e ;	0.90 (0.83, 0.98)	0.018
	Day 14		0.92 (0.85, 0.99)	0.034
11.6	Day 90		0.86 (0.72, 1.02)	0.20
IL-0	Dox 14		0.80 (0.72, 1.03)	0.11
	Day 14 Day 90		1.01 (0.87, 1.17)	0.87
IL-7	Screening		0.89 (0.75, 1.06)	0.19
	Day 14	_ _	0.89 (0.77, 1.04)	0.14
	Day 90	— • +	0.89 (0.77, 1.03)	0.12
IL-8	Screening	— — —	0.84 (0.73, 0.97)	0.020
	Day 14	—•—-i	0.86 (0.76, 0.98)	0.020
	Day 90	=!	0.97 (0.85, 1.11)	0.68
IL-10	Screening		0.80 (0.62, 1.03)	0.085
	Day 14			0.15
II -15	Screening	!	0.89 (0.82, 0.96)	0.0038
IL-IU	Dav 14	I	0.91 (0.85, 0.97)	0.0059
	Day 90	_ _	1.01 (0.95, 1.08)	0.75
IL-16	Screening	_ i	0.89 (0.82, 0.97)	0.0049
	Day 14	- - ¦	0.90 (0.84, 0.97)	0.0060
	Day 90		0.99 (0.92, 1.06)	0.80
IL-17A	Screening		0.94 (0.75, 1.19)	0.61
	Day 14		0.97 (0.79, 1.19)	0.76
	Day 90		1.13 (0.90, 1.42)	0.30
IL-18	Screening Day 14		0.97 (0.87, 1.08)	0.56
	Day 14 Day 90	- 	1.07 (0.99, 1.17)	0.70
IL-21	Screening		0.91 (0.73, 1.12)	0.37
	Day 14		0.93 (0.77, 1.12)	0.46
	Day 90		1.07 (0.89, 1.29)	0.47
IL-22	Screening		1.00 (0.75, 1.33)	0.97
	Day 14	4	0.99 (0.77, 1.28)	0.95
	Day 90		0.97 (0.76, 1.25)	0.83
IL-29/IFN-λ	Screening	_ ;	0.80 (0.67, 0.95)	0.0094
	Day 14		0.83 (0.71, 0.96)	0.013
IEN-d2a	Screening -		0.69 (0.36, 1.33)	0.87
	Day 14	_	0.76 (0.43, 1.34)	0.34
	Day 90	_	1.27 (0.64, 2.54)	0.49
IFN-γ	Screening	i	0.72 (0.54, 0.95)	0.020
	Day 14	- ¦	0.76 (0.59, 0.96)	0.022
	Day 90	-	1.01 (0.80, 1.28)	0.94
IP-10	Screening	_	0.69 (0.57, 0.83)	0.0001*
	Day 14	-	0.74 (0.63, 0.87)	0.0003*
MCD 1	Day 90		1.10 (0.93, 1.29)	0.0012*
IVICP-1	Day 14		0.65 (0.77, 0.94)	0.0012
	Day 90		1.04 (0.96, 1.13)	0.30
MIP-1α	Screening	_	0.97 (0.83, 1.14)	0.72
	Day 14	_	0.98 (0.86, 1.13)	0.82
	Day 90		1.06 (0.92, 1.21)	0.44
TNF-α	Screening	!	0.78 (0.65, 0.95)	0.012
	Day 14	— • —- ¦	0.81 (0.69, 0.96)	0.013
VE05 1	Day 90	— • • · · · ·	0.99 (0.84, 1.18)	0.94
VEGE-A	Screening		0.97 (0.82, 1.14)	0.70
	Day 14	+	0.97 (0.84, 1.12)	0.00
VCAM-1	Screening		1.02 (0.90 1.16)	0.73
1 G. UT- 1	Day 14		1.04 (0.93, 1.16)	0.51
	Day 90	I	1.12 (1.01, 1.24)	0.026
		0.4 0.6 1 1.6		
			•	
		Lower geometric mean migher geometric mean		

Supplemental Figure 7. Differences of the cytokine levels between partially and fully vaccinated participants.

Note: ratio (95% CI) of geometric mean between the partially (denominator) and fully vaccinated (numerator) in pg/mL of each cytokine and chemokine are presented.

Each analyte had a separate mixed effect model and all the models were adjusted for age, sex, BMI, hypertension, diabetes, treatment arms, and COVID-19 waves. Treatment arms were not adjusted at screening, since participants were not transfused at screening.

Among the covariates, only BMI have missing data, and the prevalence of missingness was 5%. Available case method was used to exclude missing values.

Assay	Visit	Ratio of geometric mean (95% Cl),	Ratio of geometric mean (95% CI)	P value
II-1RA	Screening		1 05 (0 90, 1 24)	0.52
	Day 14	<u>l</u>	1.03 (0.89, 1.18)	0.02
	Day 90		0.88 (0.78, 1.00)	0.70
II2RA	Screening		0.98 (0.89, 1.08)	0.65
12-2107	Day 14		0.97 (0.89, 1.05)	0.00
	Day 90	1	0.90 (0.83, 0.98)	0.40
11-6	Screening	<u> </u>	1.05 (0.85, 1.30)	0.65
12 0	Day 14		1.03 (0.85, 1.23)	0.00
	Day 90		0.91 (0.77, 1.08)	0.29
IL-7	Screening	_	0.86 (0.70, 1.04)	0.12
	Day 14	<u>_</u>	0.85 (0.72, 1.01)	0.072
	, Dav 90	_	0.83 (0.70, 0.99)	0.035
IL-8	Screening	i	0.82 (0.70, 0.97)	0.022
	Day 14	_	0.82 (0.71, 0.95)	0.0097
	Day 90	i	0.82 (0.70, 0.96)	0.015
IL-10	Screening		1.08 (0.80, 1.46)	0.62
	Day 14	i •	1.05 (0.81, 1.37)	0.70
	Day 90	e <u> </u>	0.93 (0.71, 1.21)	0.59
IL-15	Screening	_ + _	0.99 (0.91, 1.09)	0.91
	Day 14		0.99 (0.91, 1.07)	0.83
	Day 90		0.97 (0.90, 1.05)	0.49
IL-16	Screening	- <u>+</u>	1.05 (0.95, 1.15)	0.35
	Day 14		1.03 (0.94, 1.12)	0.55
	Day 90		0.93 (0.85, 1.01)	0.081
IL-17A	Screening	e	0.92 (0.70, 1.21)	0.57
	Day 14	_	0.92 (0.72, 1.18)	0.52
	Day 90		0.92 (0.70, 1.20)	0.54
IL-18	Screening	— f —	0.99 (0.88, 1.11)	0.88
	Day 14		0.98 (0.89, 1.09)	0.76
	Day 90	— • ;	0.95 (0.86, 1.05)	0.31
IL-21	Screening		0.91 (0.72, 1.16)	0.45
	Day 14	-	0.91 (0.74, 1.13)	0.42
	Day 90		0.93 (0.75, 1.17)	0.54
IL-22	Screening		0.95 (0.68, 1.34)	0.78
	Day 14		0.96 (0.71, 1.30)	0.81
	Day 90		1.02 (0.76, 1.38)	0.89
1L-29/1FIN-A	Dov 14		0.98 (0.80, 1.20)	0.00
	Day 14		0.96 (0.82, 1.17)	0.01
IENL@2a	Screening		0.89 (0.41, 1.96)	0.71
ii N-uza	Day 1/		0.93 (0.46, 1.86)	0.70
	Day 14 Day 90	i	- 1 14 (0 51 2 56)	0.75
IEN-v	Screening		1 15 (0 82, 1 60)	0.42
	Day 14	<u>i</u>	1.14 (0.86, 1.53)	0.36
	Day 90		1.13 (0.87, 1.48)	0.36
IP-10	Screening	_	0.95 (0.76, 1.19)	0.66
	Day 14	-	0.94 (0.77, 1.15)	0.56
	Day 90	_	0.91 (0.75, 1.10)	0.34
MCP-1	Screening	s [0.98 (0.87, 1.10)	0.69
	Day 14	— •	0.97 (0.88, 1.07)	0.53
	Day 90	— <u>—</u>	0.92 (0.84, 1.02)	0.098
MIP-1α	Screening	_	0.96 (0.80, 1.16)	0.68
	Day 14		0.97 (0.83, 1.15)	0.76
	Day 90		1.05 (0.89, 1.24)	0.56
TNF-α	Screening		0.88 (0.71, 1.10)	0.26
	Day 14		0.89 (0.73, 1.08)	0.25
	Day 90		0.96 (0.78, 1.16)	0.65
VEGF-A	Screening	e _ <u>+</u>	0.90 (0.74, 1.09)	0.27
	Day 14	<u>+</u>	0.89 (0.75, 1.05)	0.17
	Day 90		0.84 (0.73, 0.98)	0.024
VCAM-1	Screening	• ;	0.94 (0.81, 1.09)	0.42
	Day 14		0.93 (0.82, 1.06)	0.30
	Day 90		0.89 (0.79, 1.00)	0.059
		0.6 i 1.6		
		Lower geometric mean Higher geometric mean	•	

Supplemental Figure 8. Sensitivity analysis to compare the cytokine and chemokine levels between unvaccinated and fully vaccinated participants after censoring the visits among individuals with a change

in vaccination status.

Note: ratio (95% CI) of geometric mean between the unvaccinated (denominator) and fully vaccinated (numerator) in pg/mL of each cytokine and chemokine are presented.

Each analyte had a separate mixed effect model and all the models were adjusted for age, sex, BMI, hypertension, diabetes, treatment arms, and COVID-19 waves. Treatment arms were not adjusted at screening, since participants were not transfused at screening. Among the covariates, only BMI have missing data, and the prevalence of missingness was 5%. Available case method was used to exclude missing values.

Assay	Visit	fully vaccinated / unvaccinated	(95% CI)	P value
IL-1RA	Screening	, _	0.81 (0.70, 0.93)	0.0037
	Day 14	_ -	0.82 (0.71, 0.93)	0.0030
	Day 90	— — —i	0.84 (0.73, 0.96)	0.013
IL-2RA	Screening	e	0.84 (0.74, 0.95)	0.0065
	Day 14	— — —	0.85 (0.75, 0.96)	0.0088
	Day 90		0.89 (0.78, 1.01)	0.072
IL-6	Screening		0.87 (0.73, 1.03)	0.10
	Day 14		0.87 (0.73, 1.02)	0.085
11.7	Day 90 Screening		0.80 (0.66, 0.98)	0.097
12-7	Day 14		0.80 (0.66, 0.97)	0.020
	Day 90	i	0.79 (0.64, 0.98)	0.033
IL-8	Screening	_ 	0.62 (0.54, 0.72)	<0.0001*
	Day 14	— —	0.63 (0.55, 0.73)	<0.0001*
	Day 90	<u> </u>	0.67 (0.57, 0.79)	<0.0001*
IL-10	Screening		0.82 (0.64, 1.04)	0.11
	Day 14		0.85 (0.67, 1.07)	0.16
11.45	Day 90		1.00 (0.77, 1.31)	0.99
12-13	Day 14	 /	0.09 (0.01, 0.97)	0.010
	Day 90		0.99 (0.90, 1.09)	0.90
IL-16	Screening		0.93 (0.85, 1.03)	0.17
	Day 14		0.93 (0.85, 1.03)	0.15
	Day 90		0.92 (0.83, 1.03)	0.15
IL-17A	Screening	_	0.87 (0.68, 1.11)	0.25
	Day 14		0.90 (0.71, 1.13)	0.36
11 40	Day 90		1.06 (0.80, 1.41)	0.69
IL-10	Day 14		0.92 (0.80, 1.05)	0.20
	Day 90	_	0.95 (0.83, 1.09)	0.49
IL-21	Screening	_	0.98 (0.74, 1.30)	0.89
	Day 14	_	1.01 (0.76, 1.34)	0.94
	Day 90		1.20 (0.88, 1.65)	0.25
IL-22	Screening		1.24 (0.88, 1.74)	0.22
	Day 14 Day 90		1.23 (0.69, 1.73)	0.19
IL-29/IFN-λ	Screening		0.79 (0.65, 0.96)	0.018
	Day 14	_	0.82 (0.68, 0.99)	0.040
	Day 90	e	0.99 (0.79, 1.23)	0.90
IFN-α2a	Screening		0.59 (0.30, 1.15)	0.12
	Day 14	_	0.67 (0.35, 1.28)	0.22
IEN v	Day 90 Screening		- 1.30 (0.56, 3.03)	0.079
11 19-9	Day 14		0.87 (0.71, 1.06)	0.078
	Day 90		1.15 (0.89, 1.50)	0.29
IP-10	Screening	_ -	0.63 (0.53, 0.75)	<0.0001*
	Day 14	-	0.67 (0.57, 0.79)	<0.0001*
	Day 90		0.92 (0.76, 1.11)	0.37
MCP-1	Screening		0.79 (0.71, 0.87)	<0.0001*
	Day 14 Day 00	I	0.80 (0.72, 0.89)	<0.0001*
MIP-1a	Screening	I 	0.95 (0.79, 1.15)	0.039
	Day 14		0.98 (0.82, 1.17)	0.81
	Day 90		1.12 (0.92, 1.37)	0.24
TNF-α	Screening	e	0.63 (0.52, 0.75)	<0.0001*
	Day 14	_	0.65 (0.55, 0.77)	<0.0001*
	Day 90		0.78 (0.64, 0.95)	0.011
VEGE-A	Ocreening		0.76 (0.63, 0.92)	0.0055
	Day 14 Day 90		0.73 (0.52, 0.91)	0.0005*
VCAM-1	Screening	_ _	1.02 (0.88, 1.18)	0.80
	Day 14		1.03 (0.89, 1.18)	0.72
	Day 90		1.07 (0.91, 1.25)	0.42
		0.4 0.6 1 1.6 2.7		
		Lower geometric mean Higher geometric mean	>	

Supplemental Figure 9. Sensitivity analysis to compare the cytokine and chemokine levels between unvaccinated and fully vaccinated participants stratified by age.

Note: ratio (95% CI) of geometric mean between the unvaccinated (denominator) and fully vaccinated (numerator) in pg/mL of each cytokine and chemokine are presented.

Each analyte had a separate mixed effect model and all the models were adjusted for age, sex, BMI, hypertension, diabetes, treatment arms, and COVID-19 waves. Treatment arms were not adjusted at screening, since participants were not transfused at screening.

Among the covariates, only BMI have missing data, and the prevalence of missingness was 5%. Available case method was used to exclude missing values.

Assay	Visit	Ratio of geometric mean (95% CI),	Ratio of geometric mean	P value
11 104	Scrooning		0.85 (0.75, 0.07)	0.015
IL-IKA	Dov 14		0.85 (0.75, 0.97)	0.015
	Day 14		0.80 (0.70, 0.97)	0.011
	Day 30	1	0.89 (0.80, 0.89)	0.0079
IL-2KA	Dox 14	!	0.89 (0.81, 0.97)	0.0078
	Day 14		0.04 (0.87, 1.02)	0.0031
11.6	Scrooning		0.94 (0.07, 1.02)	0.13
IL-0	Day 14		0.94 (0.79, 1.10)	0.42
	Day 14	1	0.89 (0.77, 1.03)	0.00
11 -7	Screening	I	0.79 (0.66, 0.93)	0.0054
	Day 14	i	0.78 (0.66, 0.91)	0.0018*
	Day 90	_	0.73 (0.63, 0.86)	0.0001*
IL-8	Screening	_	0.68 (0.60, 0.79)	< 0.0001*
	Dav 14	_	0.69 (0.61, 0.79)	<0.0001*
	Day 90	_ i	0.75 (0.65, 0.85)	<0.0001*
IL-10	Screening		0.93 (0.74, 1.18)	0.57
	Day 14		0.96 (0.77, 1.19)	0.70
	Day 90		1.11 (0.88, 1.39)	0.37
IL-15	Screening		0.90 (0.84, 0.98)	0.010
	Day 14	- - -!	0.92 (0.85, 0.98)	0.017
	Day 90	-4-	0.98 (0.92, 1.05)	0.64
IL-16	Screening		0.92 (0.85, 1.00)	0.041
	Day 14	- -	0.92 (0.85, 0.99)	0.024
	Day 90		0.90 (0.84, 0.98)	0.0092
IL-17A	Screening	_	0.91 (0.72, 1.14)	0.39
	Day 14	_	0.91 (0.74, 1.13)	0.40
	Day 90		0.95 (0.75, 1.20)	0.66
IL-18	Screening	— 	0.97 (0.87, 1.08)	0.56
	Day 14		0.97 (0.88, 1.07)	0.60
	Day 90	-+-	1.00 (0.91, 1.10)	0.99
IL-21	Screening		0.82 (0.66, 1.01)	0.067
	Day 14	—— • ——•	0.85 (0.69, 1.04)	0.11
	Day 90		1.02 (0.83, 1.27)	0.83
IL-22	Screening		1.11 (0.84, 1.48)	0.47
	Day 14		1.11 (0.85, 1.45)	0.43
11 20/IENL)	Day 90		0.76 (0.64, 0.01)	0.41
1L-29/1FIN-A	Doy 14	!	0.70 (0.04, 0.91)	0.0020
	Day 14		0.08 (0.83, 1.16)	0.0040
IEN-a2a	Screening -		0.67 (0.35, 1.29)	0.01
1111420	Day 14	-	0.76 (0.42, 1.40)	0.38
	Day 90		- 1.50 (0.74, 3.04)	0.26
IFN-v	Screening	e	0.86 (0.67, 1.10)	0.22
	Dav 14		0.90 (0.72, 1.12)	0.35
	Day 90		1.19 (0.96, 1.46)	0.11
IP-10	Screening	_ i	0.66 (0.56, 0.79)	<0.0001*
	Day 14	_ _	0.70 (0.60, 0.82)	<0.0001*
	Day 90	_ [0.97 (0.83, 1.13)	0.71
MCP-1	Screening	- •	0.84 (0.76, 0.92)	0.0002*
	Day 14	- e - i	0.85 (0.78, 0.93)	0.0004*
	Day 90		0.95 (0.87, 1.03)	0.21
MIP-1α	Screening	i	0.98 (0.84, 1.15)	0.83
	Day 14	i	1.00 (0.86, 1.16)	1.0
	Day 90	- `_ •	1.10 (0.95, 1.28)	0.21
TNF-α	Screening	-	0.70 (0.59, 0.83)	<0.0001*
	Day 14	-	0.72 (0.62, 0.85)	<0.0001*
	Day 90	— — •	0.88 (0.75, 1.04)	0.12
VEGF-A	Screening	;	0.83 (0.71, 0.98)	0.026
	Day 14		0.83 (0.72, 0.97)	0.015
NOTE	Day 90	_ _	0.82 (0.72, 0.94)	0.0050
VCAM-1	Screening		0.97 (0.86, 1.10)	0.68
	Day 14		0.96 (0.67, 1.10)	0.70
	Day 90		1.00 (0.69, 1.12)	0.90
		0.4 0.6 1 1.6 2.7		
		Lower geometric mean Higher geometric mean	*	

9.B. age≥50

Assay	Visit	Ratio of geometric mean (95% CI), fully vaccinated / unvaccinated	Ratio of geometric mean (95% CI)	P value
IL-1RA	Screening	·	0.96 (0.74, 1.25)	0.76
	Daγ 14	_ !	0.96 (0.76, 1.22)	0.74
	Day 90	_	0.96 (0.80, 1.15)	0.65
IL-2RA	Screening	— <u>—</u> —	0.88 (0.75, 1.04)	0.14
	Day 14	_ _ _	0.89 (0.77, 1.04)	0.13
	Day 90	_ 	0.93 (0.82, 1.05)	0.24
IL-6	Screening	_	0.89 (0.64, 1.25)	0.51
	Day 14	_	0.91 (0.68, 1.24)	0.56
	Day 90	_ 	1.03 (0.81, 1.32)	0.80
IL-7	Screening	— —	0.71 (0.52, 0.97)	0.029
	Day 14	_	0.71 (0.54, 0.95)	0.020
	Day 90	— — —	0.73 (0.57, 0.94)	0.014
IL-8	Screening	— • _!	0.71 (0.54, 0.93)	0.013
	Day 14	— —	0.74 (0.58, 0.94)	0.014
	Day 90		0.92 (0.73, 1.15)	0.46
IL-10	Screening	e	0.64 (0.39, 1.06)	0.085
	Day 14		0.69 (0.44, 1.10)	0.12
	Day 90		1.07 (0.73, 1.59)	0.72
IL-15	Screening	—•—i	0.81 (0.69, 0.95)	0.0078
	Day 14	_ _ _!	0.83 (0.72, 0.96)	0.010
	Day 90	- 	0.95 (0.85, 1.07)	0.40
IL-16	Screening		0.95 (0.80, 1.12)	0.55
	Day 14	+	0.95 (0.81, 1.11)	0.53
	Day 90		0.96 (0.84, 1.10)	0.54
IL-17A	Screening	_	0.78 (0.50, 1.24)	0.29
	Day 14	—— • ;	0.84 (0.56, 1.28)	0.43
	Day 90		1.26 (0.86, 1.86)	0.24
IL-18	Screening	— • ;	0.89 (0.74, 1.08)	0.24
	Day 14		0.91 (0.76, 1.09)	0.31
	Day 90	_ _	1.03 (0.89, 1.19)	0.69
IL-21	Screening		0.91 (0.58, 1.41)	0.66
	Day 14	_	0.90 (0.60, 1.35)	0.61
	Day 90	•	0.87 (0.61, 1.23)	0.42
IL-22	Screening		0.55 (0.30, 0.99)	0.045
	Day 14	i	0.56 (0.33, 0.97)	0.038
	Day 90		0.66 (0.42, 1.05)	0.079
IL-29/IFN-λ	Screening		0.90 (0.64, 1.27)	0.56
	Day 14		0.91 (0.66, 1.25)	0.55
	Day 90		0.93 (0.70, 1.25)	0.65
IFN-α2a	Screening		0.47 (0.12, 1.78)	0.27
	Day 14		0.54 (0.16, 1.83)	0.32
IENI	Day 90		0.77 (0.47, 1.28)	0.77
IFIN-Y	Dov 14		0.77 (0.47, 1.26)	0.32
	Day 14		0.80 (0.51, 1.20)	0.34
ID 10	Screening		0.30 (0.07, 1.43)	0.053
11-10	Day 14	<u>I</u>	0.75 (0.54, 1.04)	0.000
	Day 90	-	1 11 (0 84 1 46)	0.000
MCP-1	Screening	I	0.80 (0.66, 0.96)	0.47
inor i	Dav 14	 _	0.83 (0.70, 0.98)	0.029
	Day 90		0.99 (0.86, 1.15)	0.94
MIP-1α	Screening	_	0.79 (0.58, 1.09)	0.15
	Dav 14	_	0.84 (0.63, 1.13)	0.24
	Day 90		1.14 (0.88, 1.47)	0.31
TNF-α	Screening	_	0.69 (0.48, 1.00)	0.049
	Day 14	<u>_</u>	0.75 (0.53, 1.05)	0.091
	Day 90		1.17 (0.88, 1.56)	0.28
VEGF-A	Screening	<u>+</u>	1.05 (0.78, 1.42)	0.73
	Day 14		1.02 (0.77, 1.35)	0.89
	Day 90	_ _	0.86 (0.68, 1.08)	0.18
VCAM-1	Screening		0.91 (0.72, 1.15)	0.44
	Day 14	_	0.92 (0.74, 1.14)	0.45
	Day 90		0.97 (0.80, 1.17)	0.74
		0.2 0.4 0.6 1 16 27		
		······································		
		Lower geometric mean Higner geometric mean		

Supplemental Figure 10. Sensitivity analysis to compare the cytokine and chemokine levels between unvaccinated and fully vaccinated participants stratified by sex.

Note: ratio (95% CI) of geometric mean between the unvaccinated (denominator) and fully vaccinated (numerator) in pg/mL of each cytokine and chemokine are presented.

Each analyte had a separate mixed effect model and all the models were adjusted for age, BMI, hypertension, diabetes, treatment arms, and COVID-19 waves. Treatment arms were not adjusted at screening, since participants were not transfused at screening.

Among the covariates, only BMI have missing data, and the prevalence of missingness was 5%. Available case method was used to exclude missing values.

Assay	Visit	Ratio of geometric mean (95% Cl), fully vaccinated / unvaccinated	Ratio of geometric mean (95% Cl)	P value
IL-1RA	Screening	_ -	0.83 (0.72, 0.96)	0.013
	Day 14	_ _	0.85 (0.75, 0.97)	0.015
	Day 90		0.94 (0.84, 1.05)	0.28
IL-2RA	Screening	- -	0.91 (0.83, 1.01)	0.065
	Day 14		0.92 (0.84, 1.01)	0.083
	Day 90	_ 	0.98 (0.90, 1.07)	0.62
IL-6	Screening	— • /	0.95 (0.78, 1.14)	0.55
	Day 14		0.95 (0.81, 1.13)	0.58
	Day 90	_ + _	1.00 (0.85, 1.18)	0.99
IL-7	Screening	— • !	0.75 (0.62, 0.90)	0.0018*
	Day 14	— •	0.75 (0.64, 0.90)	0.0013*
	Day 90	_ !	0.80 (0.68, 0.95)	0.012
IL-8	Screening	_ _	0.67 (0.57, 0.78)	<0.0001*
	Day 14	_ _	0.68 (0.59, 0.79)	<0.0001*
	Day 90		0.80 (0.68, 0.94)	0.0056
IL-10	Screening		0.90 (0.69, 1.18)	0.44
	Day 14		0.95 (0.74, 1.22)	0.071
11 15	Day 90	-	1.20 (0.90, 1.02)	0.071
IL-15	Dov 14		0.90 (0.82, 0.96)	0.017
	Day 14		1.02 (0.94, 1.10)	0.000
II -16	Screening	F #+	0.95 (0.87, 1.04)	0.00
12 10	Day 14	_ <u></u>	0.95 (0.87, 1.03)	0.21
	Day 90		0.95 (0.87, 1.04)	0.24
IL-17A	Screening		0.77 (0.60, 1.01)	0.056
	Day 14	_	0.81 (0.64, 1.04)	0.096
	Day 90	_	1.06 (0.81, 1.38)	0.67
IL-18	Screening		0.97 (0.86, 1.09)	0.59
	Day 14	—	0.98 (0.88, 1.10)	0.76
	Day 90	<u> </u>	1.07 (0.96, 1.19)	0.21
IL-21	Screening		0.83 (0.66, 1.06)	0.14
	Day 14		0.86 (0.68, 1.07)	0.18
	Day 90		0.99 (0.78, 1.25)	0.91
IL-22	Screening	e	1.00 (0.73, 1.39)	0.98
	Day 14		1.01 (0.74, 1.36)	0.97
	Day 90		1.02 (0.75, 1.39)	0.89
IL-29/IFN-A	Screening		0.77 (0.64, 0.93)	0.0068
	Day 14	I	0.00 (0.07, 0.95)	0.013
IEN-a2a	Screening		0.66 (0.32, 1.37)	0.76
ii in-uza	Day 14		0.76 (0.39, 1.51)	0.20
	Day 90		- 173 (0.80, 3.73)	0.17
IFN-y	Screening	_	0.84 (0.63, 1.12)	0.23
	Day 14		0.89 (0.69, 1.14)	0.35
	Day 90		1.20 (0.94, 1.53)	0.15
IP-10	Screening	— — !	0.62 (0.51, 0.76)	<0.0001*
	Day 14	e	0.67 (0.56, 0.80)	<0.0001*
	Day 90	_	0.99 (0.83, 1.18)	0.90
MCP-1	Screening	- -	0.83 (0.74, 0.92)	0.0008*
	Day 14	- - -	0.85 (0.77, 0.94)	0.0017*
	Day 90	#	0.98 (0.89, 1.08)	0.65
MIP-1α	Screening	-	1.00 (0.84, 1.19)	0.99
	Day 14		1.02 (0.87, 1.21)	0.78
	Day 90		1.17 (0.99, 1.38)	<0.0001*
INF-a	Dov 14		0.07 (0.55, 0.82)	0.0001
	Day 14		0.71 (0.39, 0.33)	0.0002
VEGF-A	Screening	I	0.77 (0.64 0.93)	0,0063
120. //	Day 14		0.78 (0.65. 0.92)	0.0036
	Day 90	_ i	0.79 (0.68, 0.92)	0.0031
VCAM-1	Screening	_ _	1.01 (0.87, 1.16)	0.94
	Day 14	_ _	1.01 (0.89, 1.16)	0.84
	Day 90		1.06 (0.93, 1.20)	0.39
		0.4 0.6 1 1.6 2.7		
		Lower geometric mean Higher geometric mean	`	

10B. Male

As	ssay	Visit	Ratio of geometric mean (95% CI), fully vaccinated / unvaccinated	Ratio of geometric mean (95% CI)	P value
Ш.	1RA	Screening		0.88 (0.73, 1.07)	0.22
		Day 14	<u> </u>	0.88 (0.74, 1.06)	0.18
		Day 90	- -	0.88 (0.75, 1.04)	0.12
	284	Screening	I	0.84 (0.74, 0.95)	0.02
IL-	-284	Day 14	!	0.85 (0.75, 0.95)	0.0000
		Day 14	- I 	0.00 (0.70, 0.00)	0.0047
	1.6	Screening		0.86 (0.67, 1.10)	0.020
'	L-0	Day 14		0.86 (0.68, 1.08)	0.24
		Day 14		0.00 (0.00, 1.00)	0.10
	1-7	Screening		0.04 (0.00, 1.00)	0.007
	L-7	Day 1/		0.73 (0.58, 0.93)	0.020
		Day 14		0.65 (0.52, 0.81)	0.0002
1	l -8	Screening	I	0.73 (0.60, 0.88)	0.0012*
		Dav 14	_ ¦	0.74 (0.61, 0.88)	0.0009*
		Day 90	i	0.79 (0.67, 0.95)	0.010
IL	-10	Screening	_	0.77 (0.54, 1.09)	0.14
		Day 14		0.79 (0.57, 1.09)	0.15
		Day 90	_	0.92 (0.68, 1.25)	0.60
IL	-15	Screening	_ _	0.85 (0.76, 0.95)	0.0030
		Day 14	_ !	0.86 (0.78, 0.95)	0.0036
		Day 90	- - +	0.93 (0.84, 1.02)	0.12
IL	-16	Screening	— — —•	0.88 (0.78, 0.99)	0.030
		Day 14	_ -	0.87 (0.78, 0.98)	0.018
		Day 90		0.86 (0.78, 0.96)	0.0054
IL-	-17A	Screening	_	0.99 (0.72, 1.37)	0.96
		Day 14	i	0.99 (0.73, 1.34)	0.95
		Day 90		0.99 (0.73, 1.34)	0.94
IL	18	Screening	— <u>•</u> ;	0.93 (0.81, 1.08)	0.34
		Day 14	# }-	0.94 (0.82, 1.07)	0.33
		Day 90	• <u>i</u>	0.95 (0.84, 1.08)	0.44
IL	21	Screening	B	0.80 (0.58, 1.10)	0.17
		Day 14	<u>_</u>	0.83 (0.61, 1.12)	0.21
	22	Day 90		1.00 (0.75, 1.33)	1.0
10	-22	Dev 14		0.65 (0.54, 1.26)	0.30
		Day 14		0.05 (0.57, 1.25)	0.40
11 20		Screening		0.97 (0.00, 1.37)	0.65
12-20	5/11 11-74	Day 14		0.81 (0.64, 1.03)	0.072
		Day 90		1.01 (0.79, 1.28)	0.001
IEN	J-α2a	Screening -		0.53 (0.20, 1.38)	0.00
		Day 14	_	0.59 (0.24, 1.44)	0.25
		Day 90		1.07 (0.41, 2.79)	0.89
IF	N-y	Screening	_	0.75 (0.53, 1.08)	0.12
	•	Day 14	<u>+</u>	0.79 (0.57, 1.10)	0.16
		Day 90		1.04 (0.78, 1.39)	0.80
IF	P-10	Screening	!	0.68 (0.53, 0.88)	0.0036
		Day 14	— —	0.72 (0.57, 0.91)	0.0066
		Day 90	_	1.00 (0.81, 1.23)	0.98
M	CP-1	Screening		0.82 (0.72, 0.94)	0.0029
		Day 14		0.84 (0.75, 0.95)	0.0039
		Day 90	_ _	0.93 (0.84, 1.04)	0.23
MI	Ρ-1α	Screening		0.80 (0.63, 1.01)	0.065
		Day 14		0.83 (0.66, 1.03)	0.095
		Day 90		1.00 (0.81, 1.23)	0.98
11	νF-α	Screening		0.72 (0.55, 0.93)	0.011
		Day 14	i	0.75 (0.59, 0.95)	0.015
		Day 90		0.93 (0.75, 1.16)	0.53
VE	GF-A	Screening	_	1.02 (0.82, 1.27)	0.86
		Day 14	_	1.00 (0.81, 1.23)	0.99
VC	ΔM. 1	Day 90 Screening		0.89 (0.75, 1.07)	0.22
vC	AIVI- I	Day 14		0.09 (0.75, 1.07)	0.21
		Day 14		0.90 (0.70, 1.00)	0.19
		Du, 00 -		0.02 (0.70, 1.00)	0.24
			U.4 U.6 1 1.6 2.7		
			Lower geometric mean Higher geometric mean		

5			
	Difference between un- and partially	Difference between partially and fully	Difference between un- and fully
	vaccinated	(fully minus partially)	vaccinated
Analyte	(partially minus unvaccinated)		(fully minus unvaccinated)
IL-1RA	0.0012 (0.0004, 0.0020)	-0.0009 (-0.0018, 0.0000)	0.0003 (-0.0002, 0.0008)
IL-2RA	0.0007 (0.0002, 0.0012)	-0.0004 (-0.0009, 0.0001)	0.0003 (0.0000, 0.0006)
IL-6	0.0008 (-0.0003, 0.0018)	-0.0007 (-0.0019, 0.0005)	0.0001 (-0.0006, 0.0008)
IL-7	-0.0000 (-0.0010, 0.0010)	-0.0001 (-0.0012, 0.0009)	-0.0002 (-0.0008, 0.0005)
IL-8	0.0007 (-0.0002, 0.0016)	-0.0000 (-0.0010, 0.0010)	0.0007 (0.0001, 0.0012)
IL-10	0.0020 (0.0004, 0.0035)	-0.0007 (-0.0025, 0.0010)	0.0013 (0.0002, 0.0023)
IL-15	0.0006 (0.0002, 0.0011)	-0.0001 (-0.0006, 0.0004)	0.0005 (0.0002, 0.0008)*
IL-16	0.0005 (0.0000, 0.0010)	-0.0006 (-0.0011, -0.0001)	-0.0001 (-0.0004, 0.0002)
IL-17A	0.0009 (-0.0006, 0.0024)	-0.0000 (-0.0017, 0.0016)	0.0009 (-0.0001, 0.0018)
IL-18	0.0005 (-0.0001, 0.0011)	-0.0002 (-0.0009, 0.0004)	0.0003 (-0.0001, 0.0006)
IL-21	0.0008 (-0.0004, 0.0020)	0.0001 (-0.0012, 0.0015)	0.0009 (0.0001, 0.0017)
IL-22	-0.0001 (-0.0018, 0.0016)	0.0003 (-0.0016, 0.0022)	0.0002 (-0.0009, 0.0013)
IL-29/IFN-λ	0.0012 (0.0001, 0.0022)	-0.0001 (-0.0012, 0.0011)	0.0011 (0.0004, 0.0018)*
IFN-α2a	0.0030 (-0.0015, 0.0074)	0.0012 (-0.0038, 0.0061)	0.0041 (0.0012, 0.0071)
IFN-γ	0.0017 (-0.0001, 0.0034)	-0.0001 (-0.0020, 0.0019)	0.0016 (0.0004, 0.0028)
IP-10	0.0023 (0.0010, 0.0035)*	-0.0002 (-0.0015, 0.0012)	0.0021 (0.0012, 0.0029)*
MCP-1	0.0010 (0.0004, 0.0016)*	-0.0003 (-0.0009, 0.0004)	0.0007 (0.0003, 0.0011)*
MIP-1a	0.0004 (-0.0005, 0.0013)	0.0004 (-0.0006, 0.0015)	0.0008 (0.0002, 0.0014)
TNF-α	0.0011 (-0.0000, 0.0023)	0.0004 (-0.0009, 0.0017)	0.0015 (0.0008, 0.0023)*
VEGF-A	0.0001 (-0.0008, 0.0010)	-0.0003 (-0.0013, 0.0007)	-0.0002 (-0.0008, 0.0004)
VCAM-1	0.0004 (-0.0003, 0.0012)	-0.0003 (-0.0011, 0.0005)	0.0002 (-0.0003, 0.0006)

Supplemental Table 2. Comparison of the slope of the daily changes of cytokine levels from screening to day 90 between vaccination groups.

Note: the difference in slope (95% CI) of the daily changes of \log_{10} pg/mL values of each analyte during follow up are presented. Each analyte had a separate mixed effect model and all the models were adjusted for age, sex, BMI, hypertension, diabetes, treatment arms, and COVID-19 waves. Treatment arms were not adjusted at screening, since participants were not transfused at screening. Among the covariates, only BMI have missing data, and the prevalence of missingness was 5%. Available case method was used to handle missing values.







Supplemental Figure 12. The correlation of cytokine levels at screening and days since fully vaccination among pre-enrollment fully vaccinated participants

Note: Correlation coefficient (R) were estimated using spearman rank correlation. P values were computed using asymptotic t approximation. Each dot represents the cytokine level of an individual. Blue line represents the LOESS curve.



50 100 150 200 250

Days since fully vaccinated