Long-term longitudinal comparisons of the health status and immune responses in the convalescent COVID-19 cohort and the vaccinated cohorts in Hong Kong (COVID1903003)

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- Lung function, exercise capacity & health status of the convalescent cohort.
- Antibody response in the convalescent cohort ± COVID-19 vaccination
- An age-matched cohort study comparing the humoral and cell-mediated immune responses in community subjects who have received BNT vs CoronaVac
- A RCT comparing BNT vs CoronaVac as a booster dose for community subjects with low levels of sVNT despite having received 2 doses of CoronaVac

Study Plan

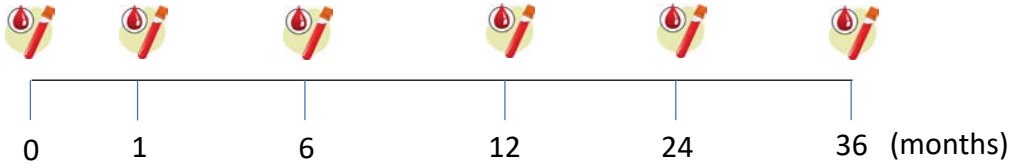
Group 1 (n=400)  Convalescent Patients

Vaccination with one dose of either Biontech or Sinovac (n = 200)

Group 2 (n>300)  BionTech cohort: mRNA vaccine

Group 3 (n>300)  Sinovac cohort: Inactivated vaccine

RCT: 3rd dose of Biontech or Sinovac (n =80) for Sinovac recipients with sVNT<60% despite having received 2 doses



Group 4 (n=100)  Healthy Controls

>18 yrs old

Cohort Recruitment sites:

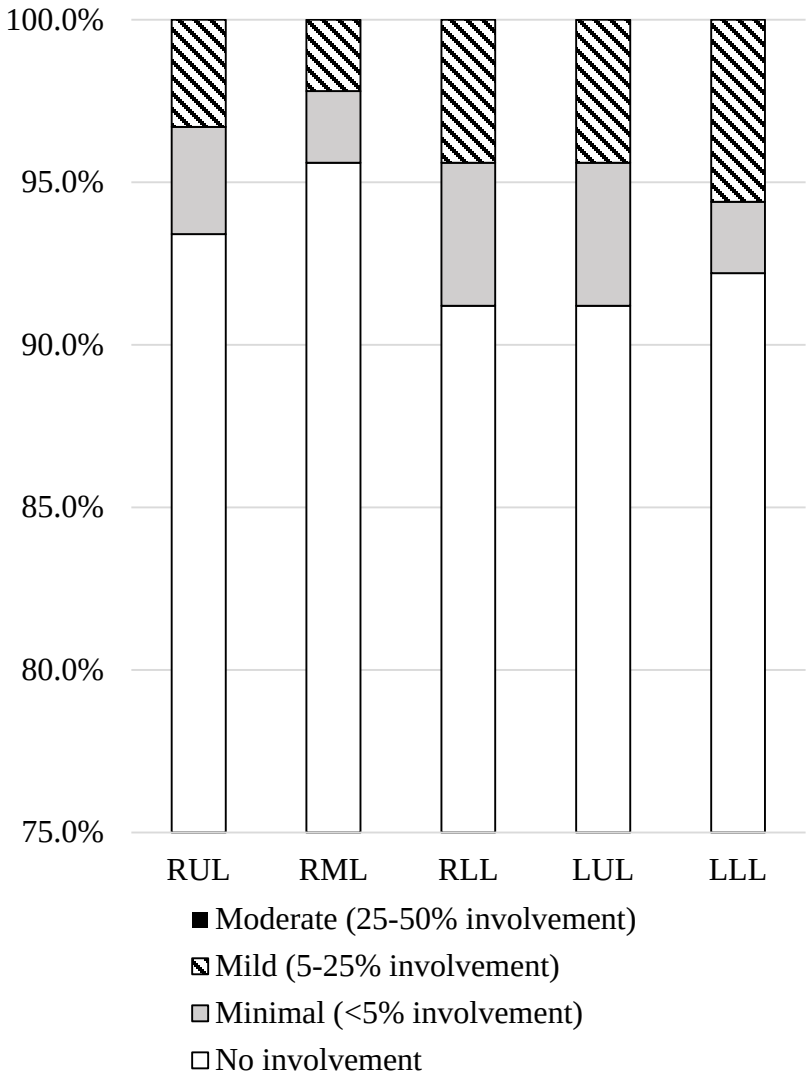
1) Convalescent Patients (PWH)
2) BionTech (CU Medical Center)
3) Sinovac (Kowloon Bay CVC, Yuen Wo Rd CVC)
4) Healthy Donors (HK Red Cross)

Table 1. Comparisons of demographics and lung function at 6 months and 12 months in COVID-19 survivors

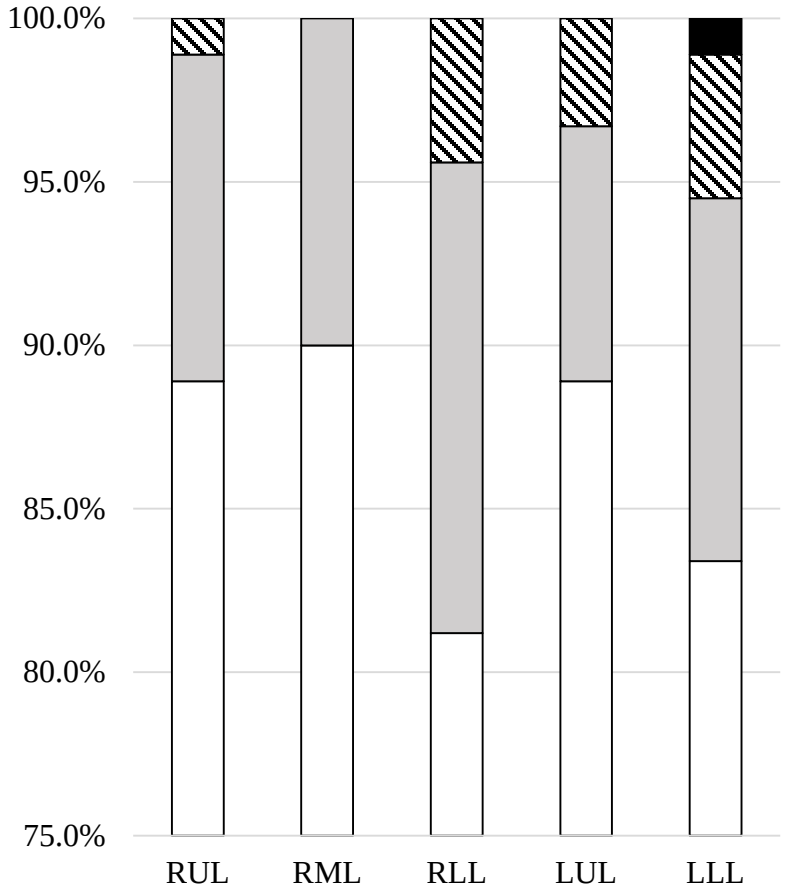
	(A) Required ICU			(B) Required O2			(C) Required mechanical ventilation			(D) Required steroid		
	Yes (n=10)	No (n=98)	95% CI between groups; p value	Yes (n=18)	No (n=90)	95% CI between groups; p value	Yes (n=9)	No (n=99)	95% CI between groups; p value	Yes (n=17)	No (n=91)	95% CI between groups; p value
Age	62.2 ± 11.9	46.6 ± 16.2	6.7 to 24.5; 0.002	62.2 ± 12.0	45.2 ± 15.8	10.2 to 23.6; <0.001	61.4 ± 12.4	46.9 ± 16.3	(4.8 to 24.4); 0.008	61.7 ± 10.9	45.5 ± 16.1	9.7 to 22.5; <0.001
Male	7	45	P=0.191	11	41	P=0.303	6	46	P=0.308	10	42	P=0.430
BMI at 6 mo, kg/m^2	26.3 ± 2.6	23.7 ± 4.1	-0.3 to 5.6; 0.080	25.6 ± 2.7	23.7 ± 4.2	-0.6 to 4.6; 0.130	26.4 ± 2.5	23.5 ± 4.1	(-0.1 to 5.8); 0.054	25.3 ± 2.8	23.6 ± 4.2	-0.5 to 3.9; 0.130
BMI at 12 mo, kg/m^2	26.1 ± 2.6	24.4 ± 4.6	-1.3 to 4.6; 0.259	26.0 ± 5.4	24.3 ± 4.2	-0.6 to 4.0; 0.143	26.5 ± 2.3	24.4 ± 4.6	(-0.9 to 5.2); 0.171	25.6 ± 3.2	24.4 ± 4.6	-1.1 to 3.6; 0.143
FEV1 at 6 mo, L	2.7 ± 0.6	2.6 ± 0.7	-0.4 to 0.7; 0.540	2.5 ± 0.6	2.6 ± 0.8	-0.5 to 0.3; 0.243	2.8 ± 0.6	2.6 ± 0.7	(-0.3 to 0.8); 0.346	2.4 ± 0.7	2.6 ± 0.7	-0.7 to 0.1; 0.188
% predicted FEV1 at 6 mo, %	105.9 ± 14.2	96.8 ± 15.7	-2.5 to 20.6; 0.122	106.0 ± 14.0	96.1 ± 15.6	0.7 to 19.2; 0.036	108.5 ± 13.0	96.7 ± 15.6	(-0.3 to 24.0); 0.056	100.2 ± 13.9	97.1 ± 16.1	-5.6 to 11.9; 0.475
FVC at 6 mo, L	3.2 ± 0.6	3.1 ± 0.8	-0.5 to 0.7; 0.751	3.0 ± 0.6	3.2 ± 0.8	-0.6 to 0.3; 0.576	3.3 ± 0.6	3.1 ± 0.8	(-0.4 to 0.8); 0.557	2.9 ± 0.8	3.2 ± 0.8	-0.8 to 0.1; 0.127
% predicted FVC at 6 mo, %	96.4 ± 10.8	96.7 ± 15.8	-11.7 to 11.1; 0.957	100.2 ± 16.8	96.0 ± 15.1	-5.1 to 13.4; 0.373	98.1 ± 10.4	96.5 ± 15.7	(-10.5 to 13.7); 0.798	94.7 ± 14.0	97.1 ± 15.7	-10.9 to 6.1; 0.580
FEV1 at 12 mo, L	2.6 ± 0.6	2.6 ± 0.7	-0.4 to 0.5; 0.879	2.4 ± 0.5	2.6 ± 0.8	-0.6 to 0.1; 0.229	2.7 ± 0.6	2.6 ± 0.7	(-0.3 to 0.7); 0.497	2.3 ± 0.6	2.6 ± 0.7	-0.7 to 0.1; 0.098
% predicted FEV1 at 12 mo, %	104.6 ± 14.3	96.1 ± 14.6	-1.1 to 18.1; 0.082	100.2 ± 15.3	96.3 ± 14.6	-3.6 to 11.4; 0.308	108.8 ± 8.4	96.1 ± 14.5	(3.0 to 22.5); 0.011	97.8 ± 15.1	96.8 ± 14.7	-6.6 to 8.8; 0.781
FVC at 12 mo, L	3.1 ± 0.6	3.1 ± 0.9	-0.5 to 0.6; 0.854	2.4 ± 0.5	2.6 ± 0.8	-0.7 to 0.2; 0.320	3.3 ± 0.7	3.1 ± 0.9	(-0.3 to 0.8); 0.409	2.8 ± 0.8	3.1 ± 0.8	-0.8 to 0.1; 0.120
% predicted FVC at 12 mo, %	97.1 ± 13.3	93.5 ± 15.8	-6.8 to 13.9; 0.496	94.1 ± 16.0	93.8 ± 15.6	-7.8 to 8.3; 0.954	101.9 ± 6.3	93.5 ± 15.8	(2.9 to 13.9); 0.005	91.1 ± 15.2	94.4 ± 15.7	-11.4 to 5.0; 0.434

Distribution and severity of involvement on HRCT chest at 1 year by ground glass opacity (A), fibrosis (B) and parenchymal changes (C).

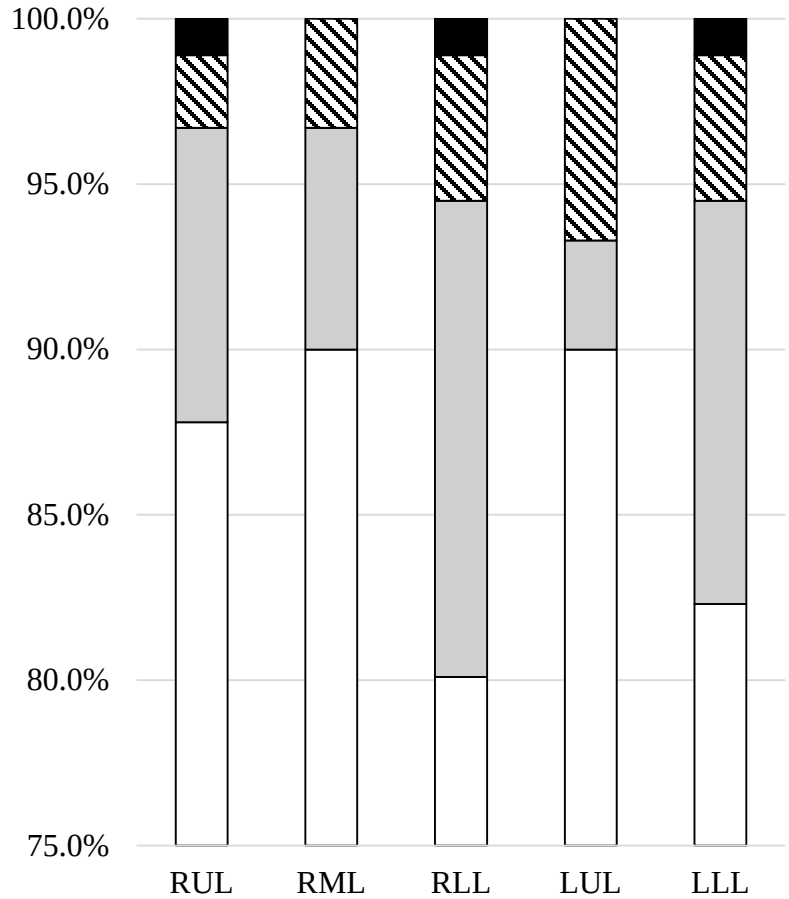
A) Severity of involvement by ground glass opacity



B) Severity of involvement by fibrosis



C) Severity of involvement by parenchymal changes



Frequency of lung function parameters below normal range in COVID-19 patients (n=235)

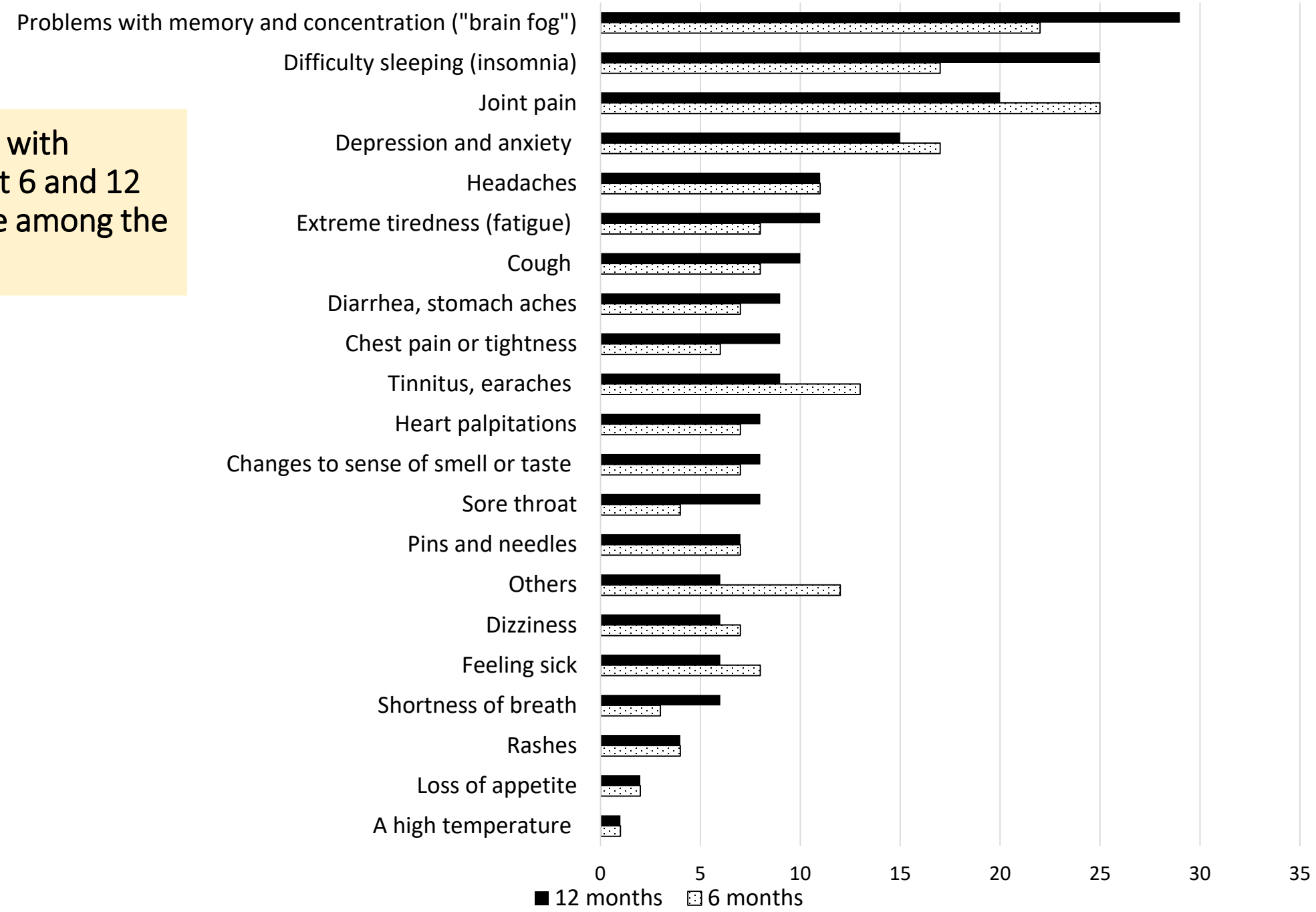
	N < 80% predicted value	N < 70% predicted value	N < 60% predicted value
FVC	45 (19.1%)	18 (7.7%)	6 (2.6%)
FEV1	28 (11.9%)	11 (4.7%)	0 (0%)

6MWD among COVID-19 and SARS survivors at 6 months and 12 months after illness in comparisons with HK normative data.

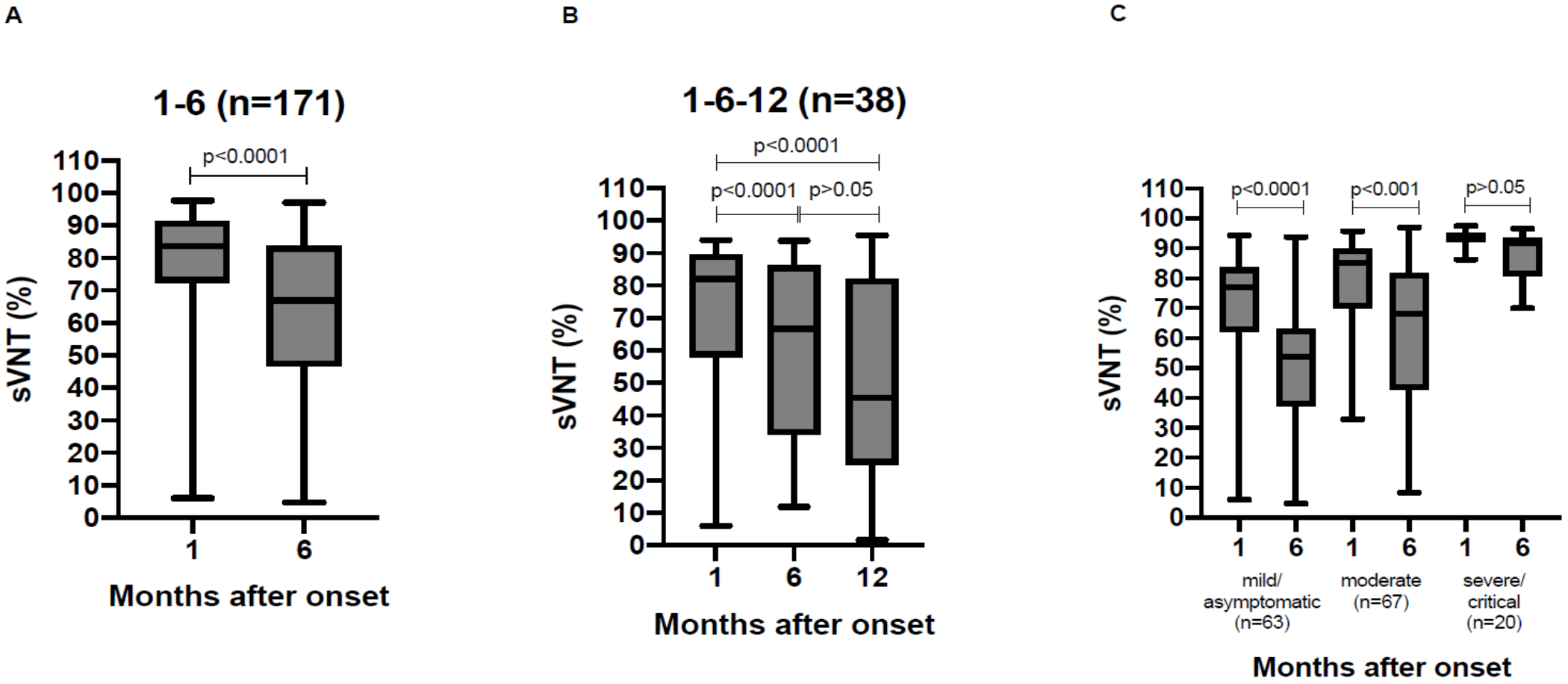
*denotes p<0.05, **p<0.01, ***p<0.001 comparing with normative data

			6 months						12 months			
	Normal		COVID		SARS		COVID vs SARS		COVID	SARS	COVID vs SARS	
Age group	n	mean ± SD	n	mean ± SD; mean Δ (vs normal) (95% CI)	n	mean ± SD; mean Δ (vs normal) (95% CI)	Mean Δ (95% CI)	P value	mean ± SD; mean Δ (vs normal) (95% CI)	mean ± SD; mean Δ (vs normal) (95% CI)	Mean Δ (95% CI)	P value
21-30												
Male	80	651 ± 105	11	445 ± 43; -206 (-242 to -171) ***	14	543 ±72; -108 (-166 to -50) ***	-98 (-149 to -47)	0.001	443 ± 47; -208 (-246 to -170) ***	538 ± 39; - 113 (-145 to -81) ***	-95 (-131 to -59)	<0.001
Female	85	600 ± 84	4	448 ± 52; -152 (-237 to -68) ***	15	490 ± 99; -110 (-158 to -62) ***	-42 (-151 to 66)	0.421	437 ± 78; -163 (-247 to -78) ***	516 ± 89; -84 (-131 to -37) ***	-79 (-182 to 25)	0.128
31-40												
Male	78	645 ± 93	5	414 ± 54; -231 (-315 to -147) ***	18	551 ± 98; -94 (-143 to -45) ***	-137 (-233 to -41)	0.007	447 ± 60; -198 (-281 to -114) ***	561 ± 89; -84 (-132 to -36) ***	-114 (-202 to -25)	0.014
Female	108	606 ± 86	15	376 ± 51; -230 (-279 to -181) ***	22	507 ± 49; -99 (-126 to -72) ***	-131 (-165 to -97)	<0.001	406 ± 42; -200 (-236 to -164) ***	517 ± 55; -89 (-118 to -60) ***	-111 (-145 to -77)	<0.001
41-50												
Male	38	623 ± 80	6	410 ± 60; -213 (-284 to -142) ***	5	544 ± 132; -79 (-247 to 89)	-134 (-269 to 1)	0.051	430 ± 36; -193 (-255 to -130) ***	542 ± 97; -81 (-160 to -29) *	-111 (-229 to 7)	0.060
Female	79	541 ± 67	6	386 ± 52; -155 (-210 to -101) ***	14	468 ± 78; -73 (-114 to -32) ***	-83 (-156 to -9)	0.031	451 ± 70; -90 (-144 to -35) **	467 ± 104; -74 (-136 to -12) **	-8 (-107 to 91)	0.865
51-60												
Male	23	588 ± 68	10	453 ± 54; -135 (-179 to -91) ***	2	405 ± 89; -183 (-289 to -78) **	48 (-52 to 149)	0.310	460 ± 39; -128 (-158 to -99) ***	459 ± 178; -129 (-1727 to 1469)	1 (-1534 to 1536)	0.996
Female	33	534 ± 89	13	393 ± 43; -141 (-173 to -110) ***	7	362 ± 109; -172 (-250 to -94) ***	30 (-71 to 132)	0.506	401 ± 38; -133 (-165 to -102) ***	401 ± 92; -133 (-208 to -58) **	0 (-86 to 85)	0.990
61-70												
Male	4	484 ± 90	12	386 ± 85; -98 (-150 to -47) **	--	--		--	415 ± 59; -69 (-120 to -17) **	--		--
Female	14	432 ± 54	11	339 ± 59; -93 (-127 to -60) ***	--	--		--	361 ± 71; -71 (-104 to -37) ***	--		--

Percentage of patients with persistent symptoms at 6 and 12 months after discharge among the COVID-19 survivors.



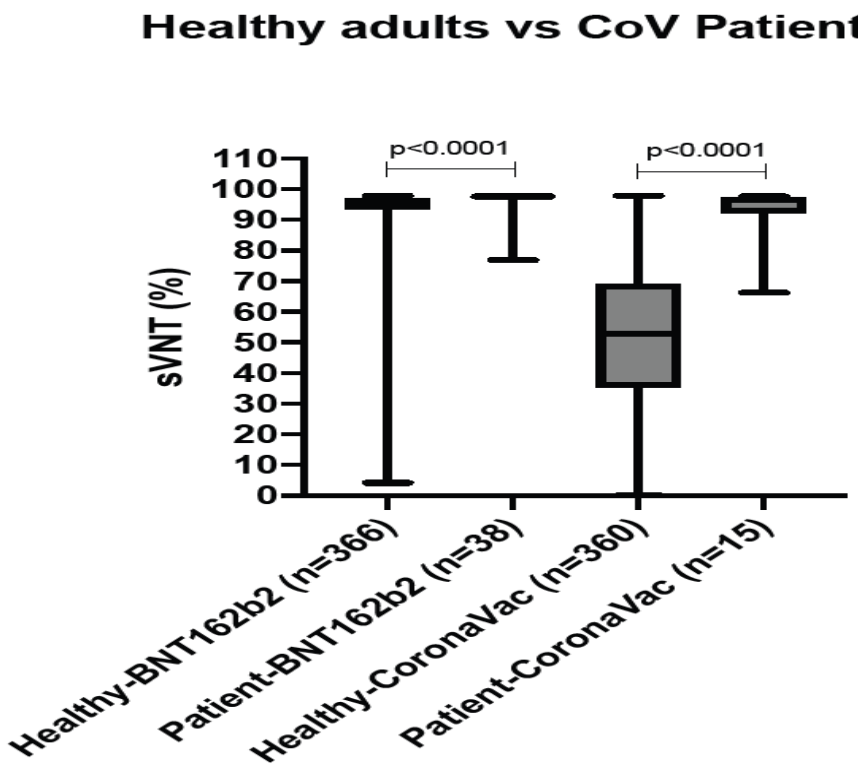
Convalescent cohort without vaccination

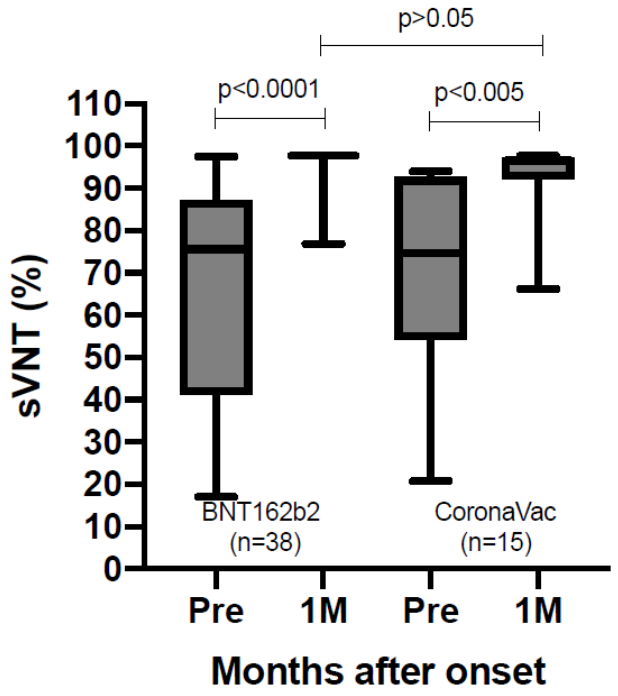


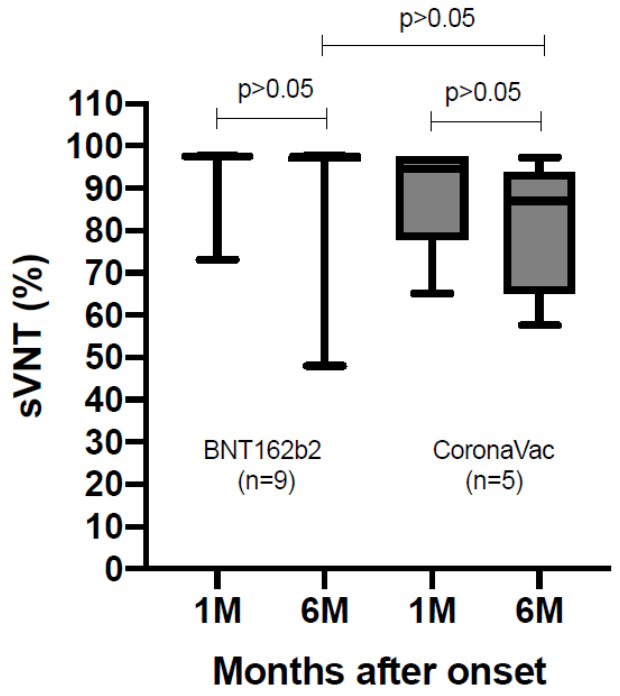
Waning of neutralizing antibody (sVNT) among the convalescent COVID-19 patients with time

Convalescent patients with history of more severe COVID-19 disease showed higher sVNT levels at 6 months after symptom onset

Patients after recovery from COVID-19 have high levels of sVNT at 6 months after receiving one dose of either Biontech or CoronaVac



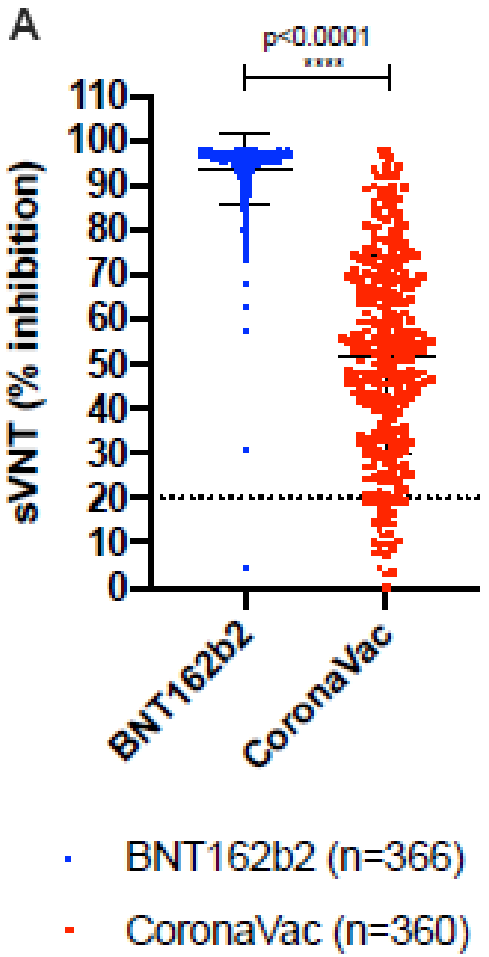




Summary: convalescent cohort

- Most survivors have normal lung function at 6 and 12 months
- HRCT chest revealed mostly minor extent of abnormalities in $< 20\%$ of patients at 1 yr.
- 6 min walk distance lower than normative data at 6 and 12 months.
- Waning of sVNT levels with time. Those with more severe disease have higher sVNT levels at 6 months
- High level of sVNT levels at 6 months after receiving one dose of either BNT or coronaVac

Vaccinated cohorts



1 month after the 2nd dose

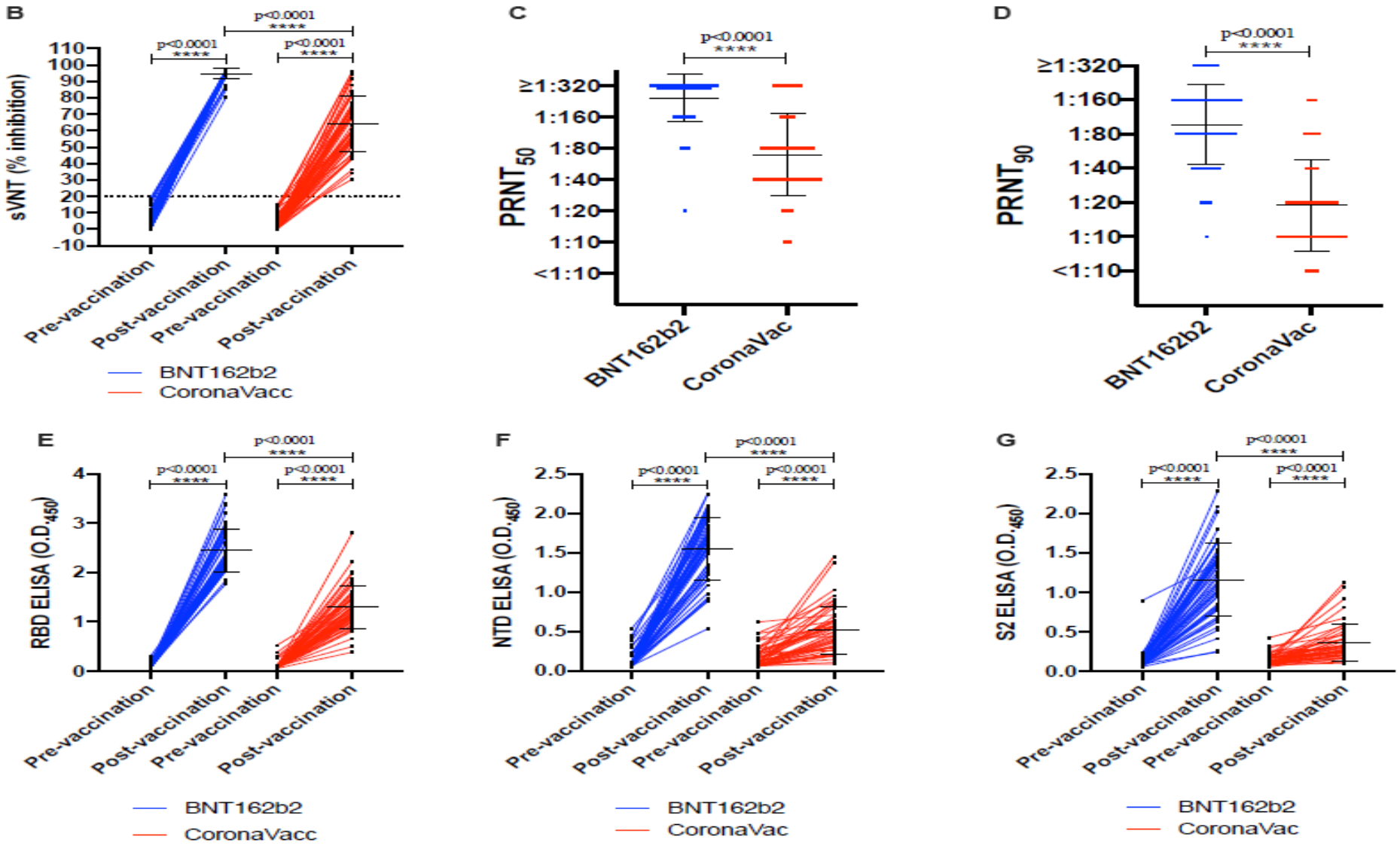
Mok C, et al. Respirology 2021

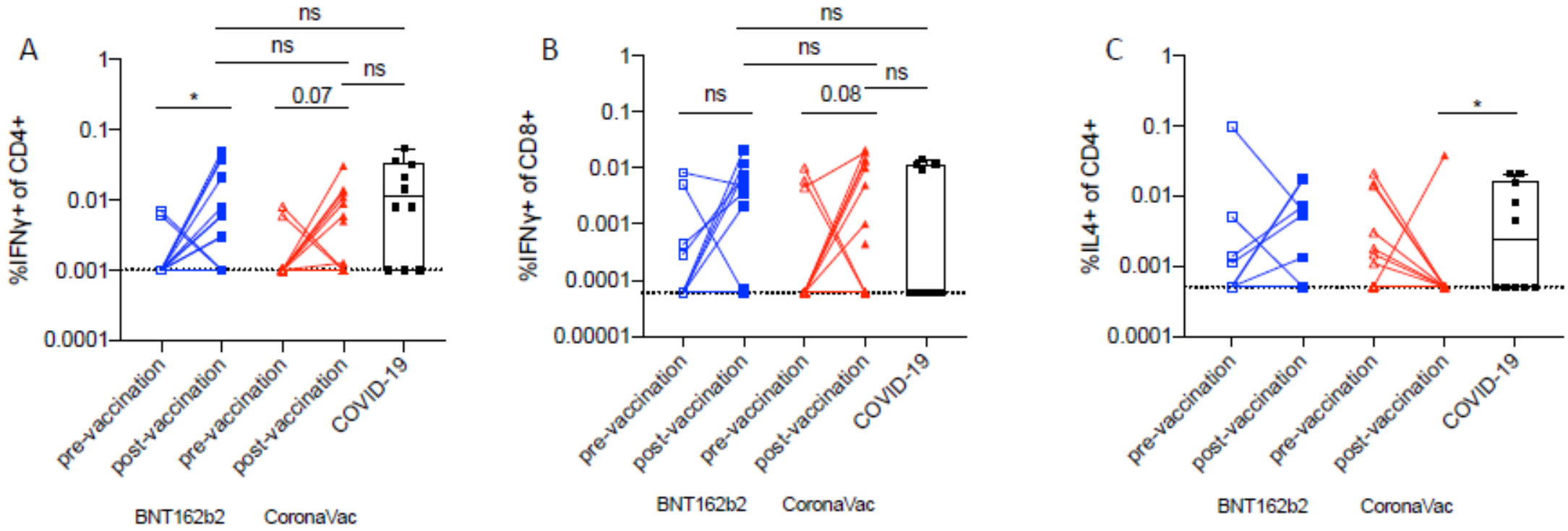
	Biontech	Sinovac	p	Test used
n	366	360		
Age (mean ± SD)	45.01 ± 13.16	51.77 ± 9.91	<0.001	Independent t-test
Gender				
Male	*142*	*123*	0.217	Fisher's exact test
Female	*224*	*237*		
Frequent smoker				
Yes	*17*	*25*	0.205	Fisher's exact test
No	*349*	*335*		
Alcohol intake				
Always	*5*	*4*	0.417	Chi-square test
Sometimes	*157*	*138*		
Never	*204*	*218*		
Cardiovascular disease	23	22	1.000	Fisher's exact test
DM	18	23	0.424	Fisher's exact test
Chronic respiratory diseases	5	5	1.000	Fisher's exact test
Resting schedule				
Regular	*180*	*161*	0.480	Chi-square test
Always insomnia / sleep late	*30*	*31*		
Sometimes insomnia / sleep late	*156*	*168*		
Regular exercise				
Yes	*188*	*166*	0.159	Fisher's exact test
No	*178*	*194*		
Flu vaccine before	220	204	0.367	Fisher's exact test

An age matched control study: At one month after the second dose of vaccination, Biontech vaccines elicited significantly higher neutralizing antibodies than CoronaVac. *Mok C, et al. Respirology 2021 (accepted)*

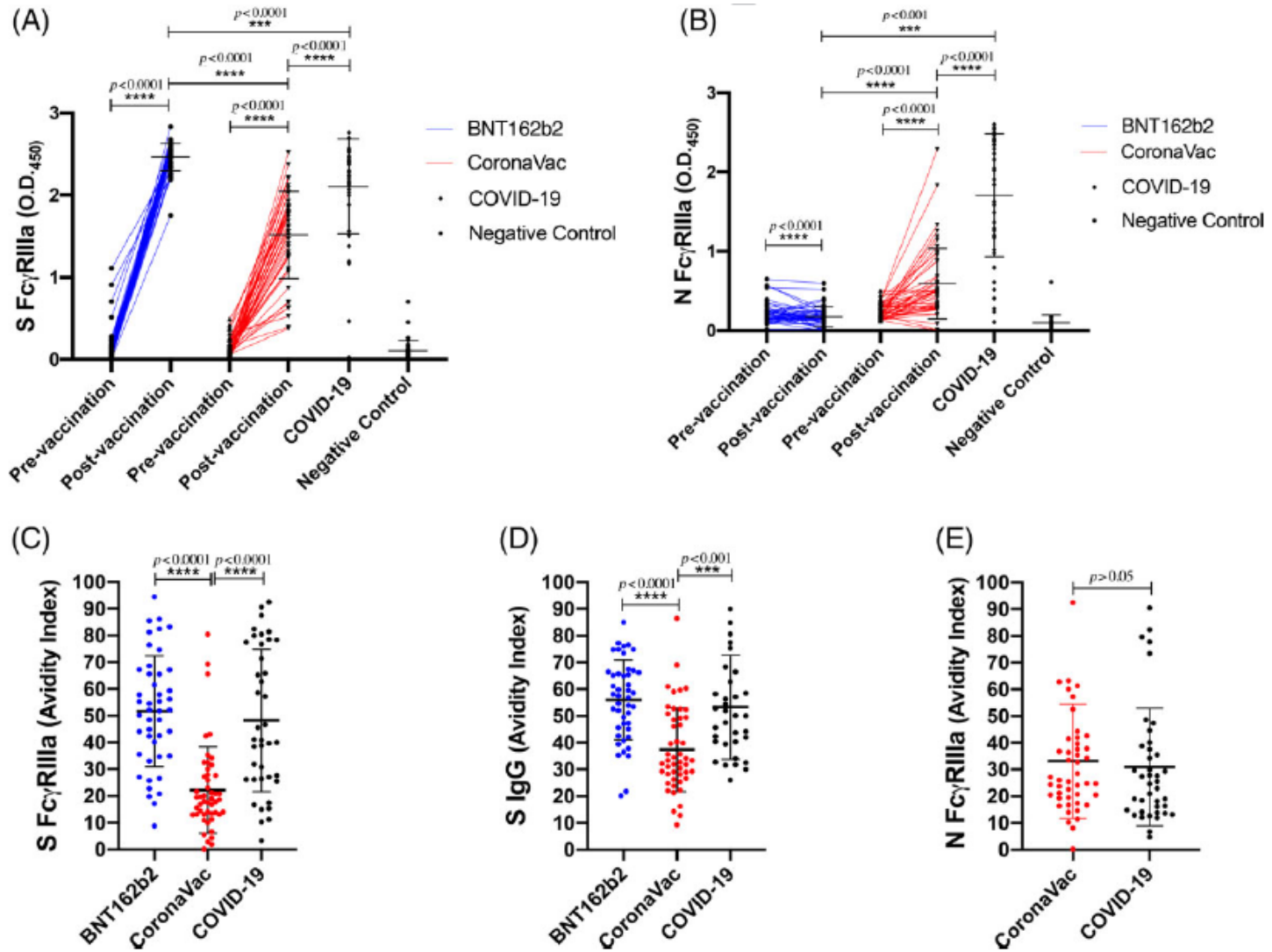
N=49 vs 49
Age matched 51.4(8.3) yrs.
The geometric mean $PRNT_{50}$ titres in those vaccinated with BNT162b2 & CoronaVac vaccines were 251.6 and 69.45 while $PRNT_{90}$ titres were 98.91 and 16.57, respectively.

48/49 (98%) of subjects vaccinated with BNT162b2 and 44/49 (89.8%) vaccinated with CoronaVac achieved the 50% protection threshold for $PRNT_{50}$.





Both vaccines resulted in comparable levels of IFNγ^+ CD4$^+$ and CD8$^+$ T cell responses to spike peptides at 1 month post-vaccination. *Mok C, et al. Respirology 2021 (accepted)*

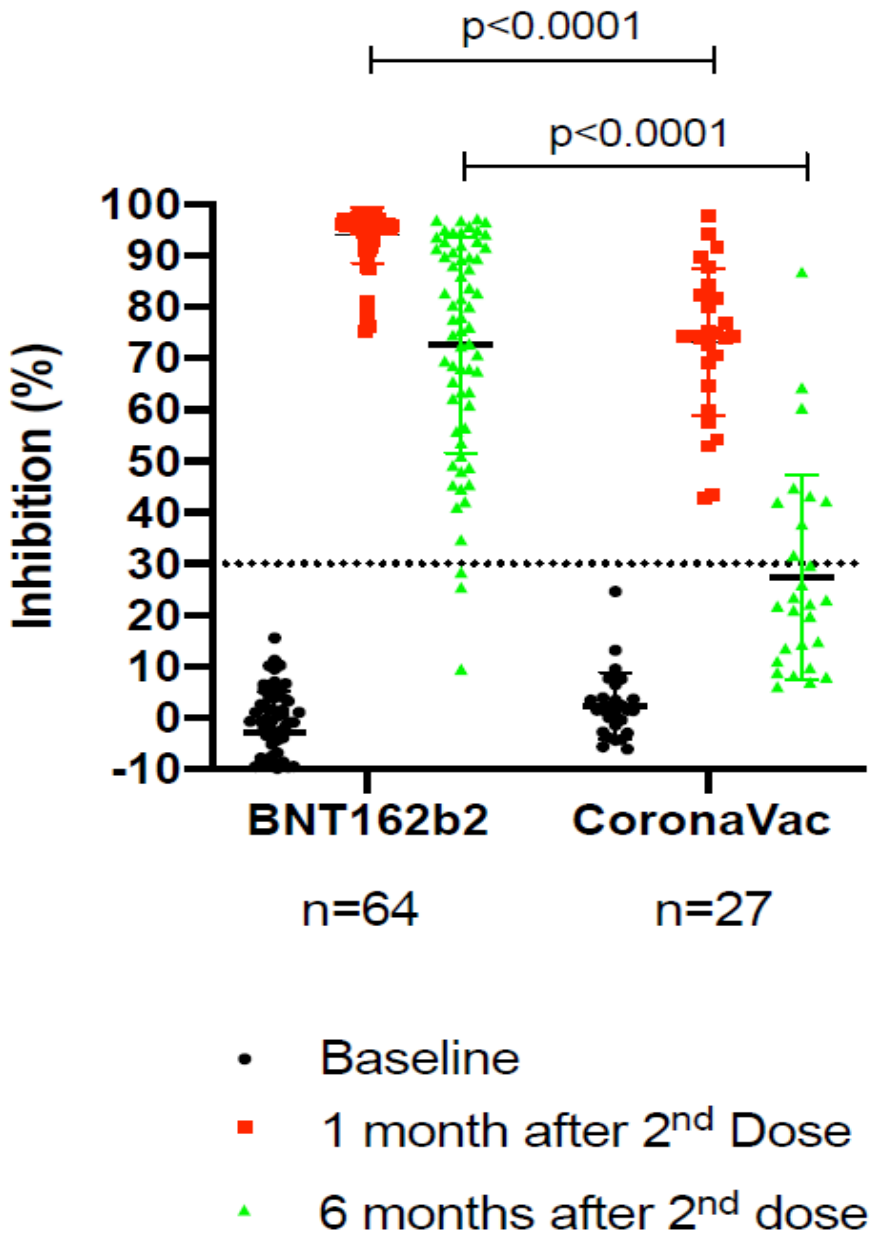


CoronaVac elicit higher structural protein specific CD4+ and CD8+ T cell responses. Mok C, et al. Respirology 2021 (accepted)

FIGURE 2 FcγRIIIa-binding antibodies and IgG avidity in the BNT162b2 and CoronaVac groups. The levels of FcγRIIIa-binding antibodies and their avidity were detected from the plasma collected from adult individuals who received two doses of BNT162b2 ($n = 49$) or CoronaVac ($n = 49$). Recovered COVID-19 cases ($n = 34$, timepoint 56 ± 17 days post infection [mean ± SD]) and healthy adults negative for SARS-CoV-2 ($n = 40$) served as positive and negative controls, respectively. The levels of (A) FcγRIIIa-binding S antibodies and (B) FcγRIIIa-binding N antibodies were tested from the plasma collected before and at 1 month after two doses of vaccination. The avidity indexes of (C) S FcγRIIIa, (D) S IgG and (E) N FcγRIIIa were determined as the proportion of antibodies remaining after 3× washes with 8 M urea compared to the total FcγRIIIa-binding antibodies to each protein. ***$p < 0.001$; ****$p < 0.0001$

Mok C, et al. Respirology 2021 (accepted)

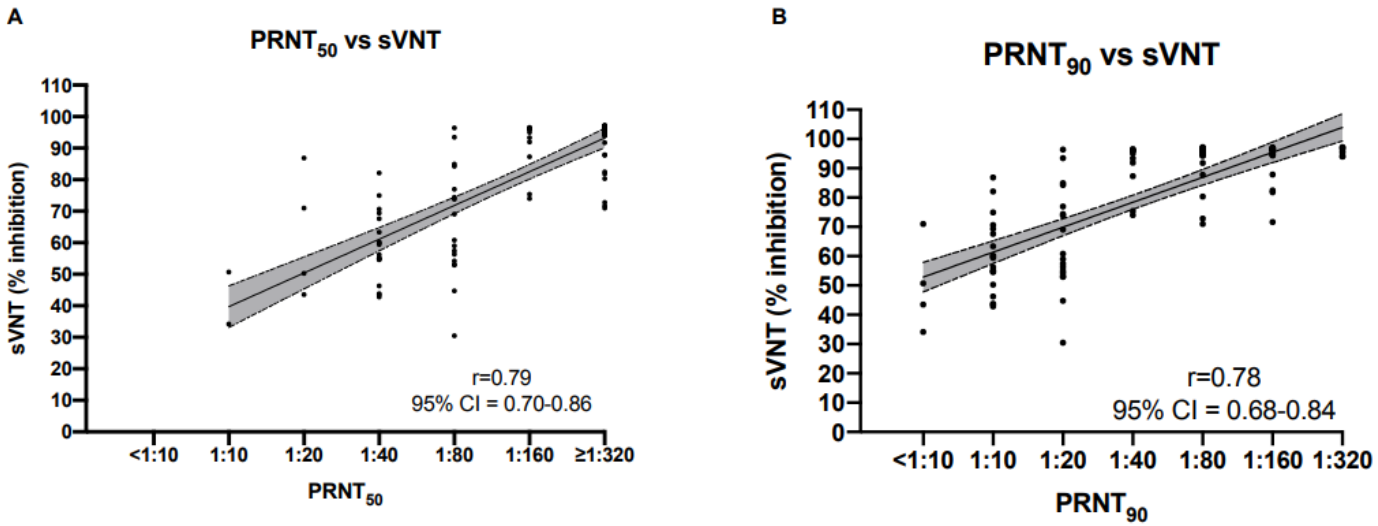
Side effects	Biontech	Sinovac	
n	49	49	p (Fisher's Exact test)
Fever	9	0	0.003
Headache	*10*	*4*	0.147
Body aches	*22*	*7*	0.002
Fatigue	28	13	0.004
Loss of appetite	*2*	*0*	0.495
Sore throat	*0*	*0*	--
Cough	*0*	*0*	--
Stuffy nose	*1*	*0*	1
Runny nose	*0*	*1*	1
Vomiting	*0*	*0*	--
Stomach ache	*0*	*0*	--
Diarrhoea	*1*	*1*	1
Pain at injection site	*34*	*13*	<0.001
Claimed no side effects	*5*	*26*	<0.001



sVNT levels dropped much more in community subjects who had received 2 doses of CoronaVac vs Biontech at 6 months

Thus a RCT of a booster dose of either Biontech or CoronaVac would be of interest for community subjects who had sVNT <60% despite having received 2 doses of CoronaVac

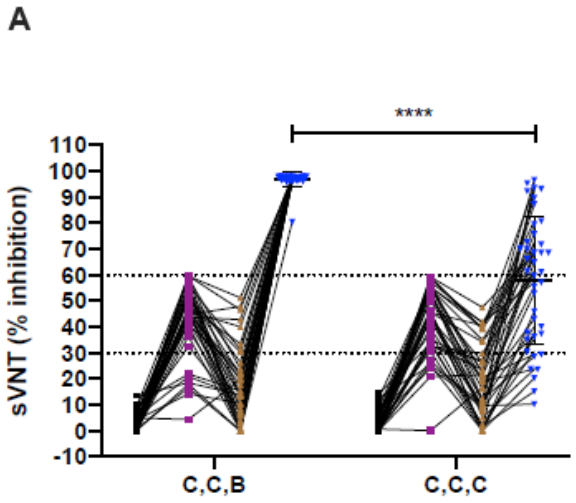
RCT: Biontech vs CoronaVac as a booster dose for CoronaVac recipients with sVNT<60% despite having received 2 doses:



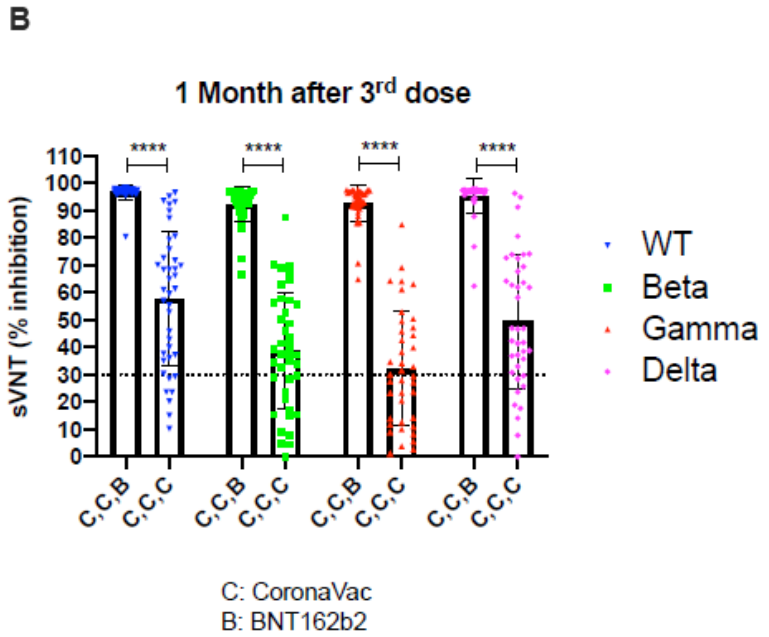
Sample size calculation. The sample size was calculated based on our previous study (Mok C, et al. Respirology 2021). The standard deviation of % inhibition in the sVNT test in the post-vaccine plasma from our age-matched cohorts for BNT1626 and CoronaVac were 3.45 and 16.72 respectively. A sample size of 32 patients in each group was estimated to have 90% power to detect a difference of 10% in sVNT by using a two-sided, unpaired t-test. As the antibody response after the booster dose is unclear, we chose a conservative sample size of 40 in each group.

- Khoury et al provided data to suggest that a 50% protection from neutralization was related to antibody levels that are 20% of convalescent antibody titers (Nature Med 2021).
- The threshold for 50% protection from re-infection using our PRNT50 assay was estimated to be a titre of 1:26 (20% of convalescent antibody titer).
- Since there will be waning of antibody from the peak titres observed at 1 month post second dose of vaccine, we set the target titre to be achieved at 1 month post-second dose of vaccine to be twice the 50% protection titre, i.e 1:52.
- This corresponds to a sVNT inhibition of 60%. Thus, we have invited recipients of CoronaVac with sVNT of <60% to take part in the booster dose RCT.

RCT
N=40 CCB vs 40 CCC

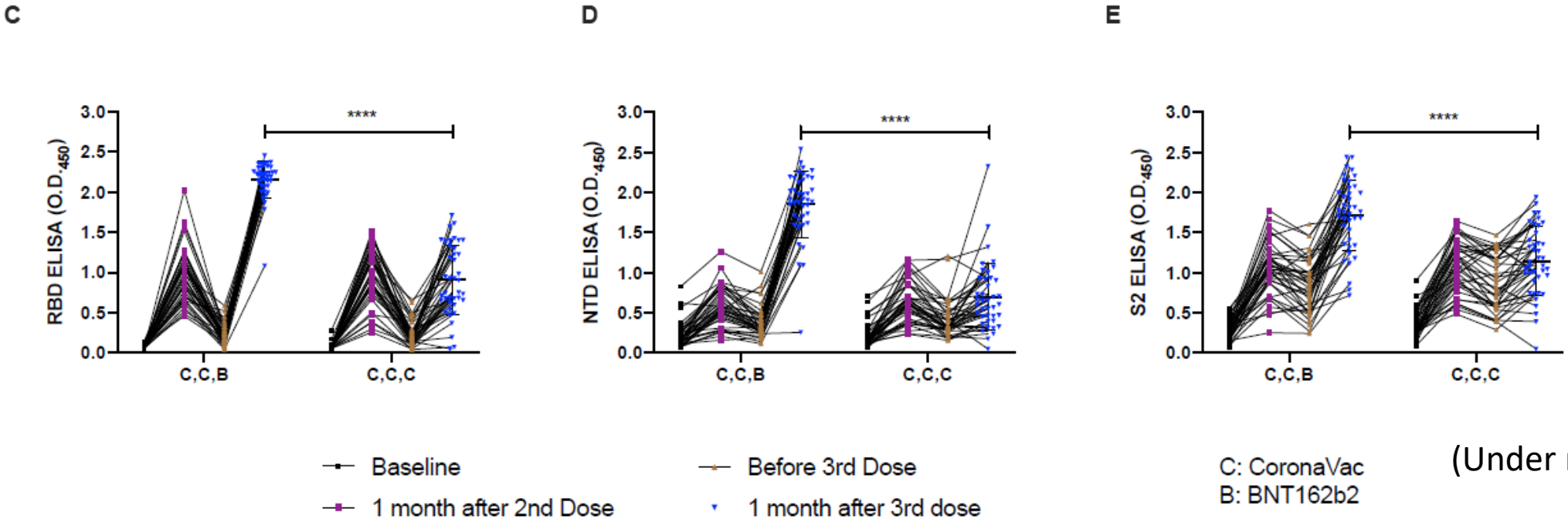


C: CoronaVac
B: BNT162b2



C: CoronaVac
B: BNT162b2

RCT: A BNT162b2 booster dose for those who poorly responded to the previous vaccination of CoronaVac is significantly more immunogenic than a CoronaVac booster . BNT162b2 also elicits higher level of SARS-CoV-2 specific neutralizing antibodies to different VOC.



C: CoronaVac
B: BNT162b2

(Under review)

The adverse reactions were only mild and short-lived.

(Under review)

	BNT162b2	Coronavac	
n	40	40	p-value
Age (Mean ± SD)	50.71±9.23	51.50±8.83	0.694
Gender			
Male	16	12	0.485
Female	25	28	
Days between 2nd and 3rd dose	111.10	115.95	0.478
Local reactions			
Pain	*35*	*12*	<0.001
Erythema	*2*	*0*	0.494
Pruritus	*3*	*1*	0.616
Swelling	*15*	*4*	0.008
Total cases reported for local reactions	*36*	*15*	<0.001
Systemic reactions			
Fever	*7*	*1*	0.057
Fatigue	*24*	*10*	0.003
Diarrhoea	*1*	*0*	1
Muscle pain	*13*	*4*	0.027
Nausea	*2*	*0*	0.494
Headache	*10*	*3*	0.067
Cough	*2*	*2*	1
Anorexia	*4*	*1*	0.359
Hypoesthesia	*4*	*0*	0.116
Dizziness	*6*	*2*	0.264
Abdominal distention	*1*	*0*	1
Peripheral oedema	*1*	*0*	1
Abdominal pain	*1*	*0*	1
Vomiting	*0*	*0*	-
Drowsiness	*11*	*8*	0.601
Joint pains	*6*	*3*	0.482
Rash	*2*	*0*	0.494
Palpitation	*5*	*2*	0.432
Total cases reported for systemic reactions	*32*	*24*	0.096

Summary: Vaccinated cohorts

- At 1 month after the 2nd dose of vaccination, Biontech vaccines elicited significantly higher neutralizing antibodies than CoronaVac. Both vaccines resulted in comparable levels of IFNγ^+ $CD4^+$ and $CD8^+$ T cell responses to spike peptides. CoronaVac elicit higher structural protein specific CD4 and CD8 T cell responses.
- sVNT levels dropped much more in community subjects who had received 2 doses of CoronaVac vs Biontech at 6 months.
- RCT: A Biontech booster dose for those who poorly responded to 2 doses of CoronaVac is significantly more immunogenic than a CoronaVac booster . BNT162b2 also elicits higher level of SARS-CoV-2 specific neutralizing antibodies to different VOC. Side effects mild and transient.