INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

April 2021

Comic Corner

Response To Reviewers – Politeness Can Take Us A Long Way

Sports & Lifestyle

Fasting And Exercise During Ramadan Time

Science Corner

SARS-CoV-2 Variants of Concern vs. Current Vaccines

NATIONAL INSTITUTE OF HEALTH RESEARCH AND DEVELOPMENT
MINISTRY OF HEALTH REPUBLIC OF INDONESIA
2021

Eid Mubaral to You All

MAY THIS DAY BE AN EXCEPTIONAL ONE FOR YOU AND YOUR LOVELY FAMILY. MAY THIS EID BRING YOU LOTS OF JOYFUL MOMENTS TO CHERISH FOREVER!

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ANNOUNCEMENT

The First Webinar series, "Updates on COVID-19 Vaccine", was held on Saturday, April 10, 2021. This webinar is supported by INA-RESPOND and partners. If you missed the event, you can watch the recording or download the presentation materials by going to our website (https://ina-respond.net/2021/03/30/webinar-series/) Thank you!

-***INA-RESPOND Webinar Series Committee***-

INA-RESPOND

Newsletter

TRIPOD, PROACTIVE, & ORCHID Study Updates

By: Eka Windari R., Lois E. Bang, Melinda Setiyaningrum, Retna Mustika Indah, Riza Danu Dewantara

STUDY UPDATES

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Per 13 April 2021, the total ongoing participants in the TRIPOD study are 3 out of 490 enrolled participants. From those three ongoing participants, they are waiting for a 6-month post-treatment visit. Two hundred and fifty-one participants have completed the study, while 236 participants are terminated early (including death). Therefore, there are still 0.61 % participants from the total enrolled participants in the follow-up status. From the uploaded CRFs, all participants from sites 520, 560, 570, and 590 have been completed the study, while 3 participants from site 580 (RSUP dr. Sardjito Jogjakarta) still need to be followed up. The Source Document Worksheet has been completed and uploaded from sites 520, 550, 560, 590, and 600.

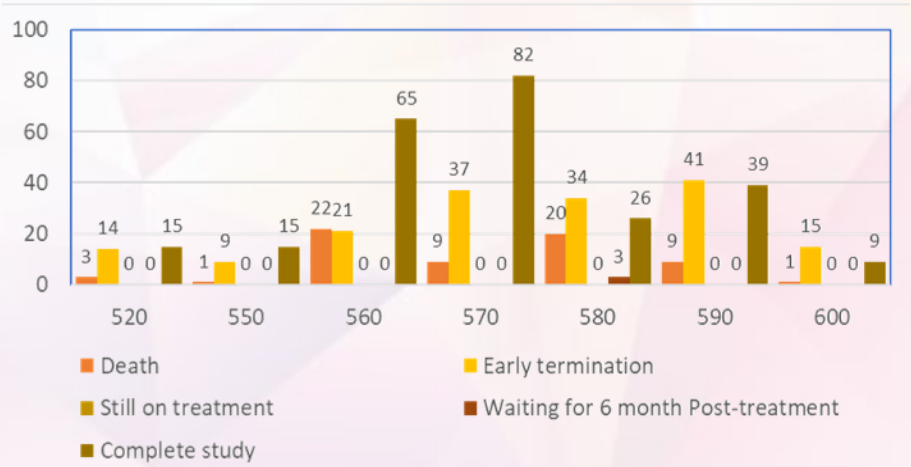

Figure 1. Participant status per site based on uploaded CRF per 25 March 2021

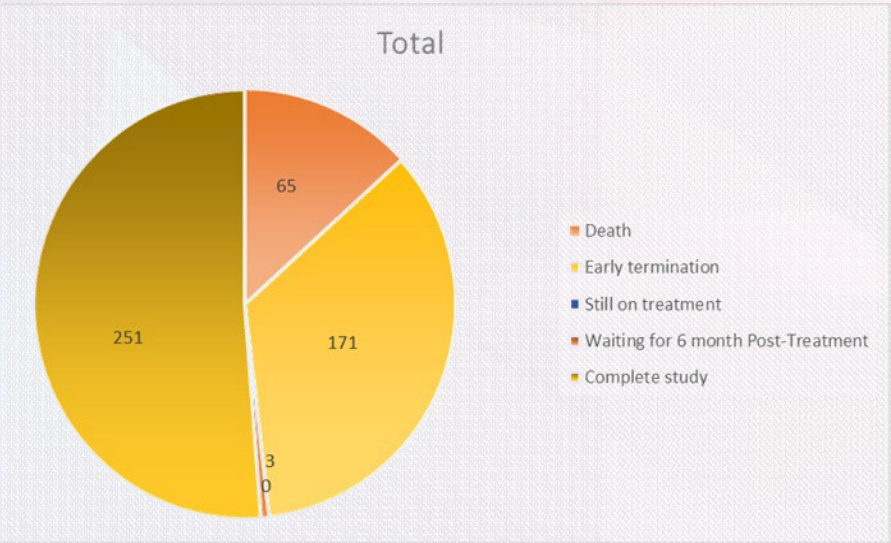

Figure 2. Total participant status based on uploaded CRF per 25 March 2021

The database Quality assurance (except for TB Treatment pages) has been conducted for sites 520, 560, 570, and 590. The Quality assurance for site 560 was conducted on 29-30 March 2021 and 2-17 April 2021.

The Site Close-out Visit (SCV) was conducted for site 520 on 30 November – 1 December 2020, site 570 on 15-16 December 2020, site 590 on 19-20 January 2021, and site 560 on 20-21 April 2021.

The TRIPOD isolate has been sent to Central Laboratory in Padjajaran University Bandung on 12 April 2021 for doing the subculture.

AWAITING CULTURE AND DST RESULT

The result for baseline culture and DST results from all sites are complete.

There are 22 subjects from three sites that have completed the last Follow Up Month 36; one subject at Site 550 (Wahidin hospital), one subject at Site 570 (Soetomo Hospital), and 20 subjects at Site 610 (Tangerang Hospital) based on the latest data per 19 April 2021.

According to the data on 19 April 2021, from 4,336 subjects enrolled, 246 subjects are 'End of Study' due to some reasons: 171 subjects' death, 23 subjects move away to the city which site PROACTIVE is not available, 25 subjects withdrew, and five subjects with negative HIV test result. To date, there are 4,085 active subjects in this study. Below is the Chart of Enrolled and Active Participants by Sites:

No	Site# / Name	1st Enrollment	Enrollment stop	# Enrolled			Participants Transfer In	Participants Transfer Out	End of Study Participants	Active Participants	
				Ped	Adult	Total					
1	510 – Hasan Sadikin	7-Feb-19	31-Dec-19	10	198	208	3	3	4	204	98.08%
2	520 – Sanglah	7-Nov-19	30-Jun-20	5	138	143	2	2	1	142	99.30%
3	530 – Cipto M.	3-May-18	31-Aug-19	36	274	310	6	3	13	300	96.77%
4	540 – Sulianti Saroso	25-Feb-19	31-Dec-19	20	162	182	0	1	4	177	97.25%
5	550 – Wahidin	14-Mar-18	31-Aug-19	10	327	337	0	0	23	314	93.18%
6	560 – Kariadi	14-Aug-18	31-Aug-19	12	218	230	3	2	12	219	95.22%
7	570 – Soetomo	26-Apr-18	31-Aug-19	6	307	313	4	3	34	280	89.46%
8	580 – Sardjito	14-Sep-18	30-Sep-19	4	216	220	2	3	4	215	97.73%
9	590 – Persahabatan	19-Jul-18	31-Aug-19	10	239	249	2	2	31	218	87.55%
10	600 – Adam Malik	12-Mar-18	31-Aug-19	2	336	338	6	5	21	318	94.08%
11	610 – Tangerang	10-Jan-18	31-Aug-19	17	310	327	0	1	41	285	87.16%
12	630 – Ansari Saleh	17-Jul-18	31-Aug-19	9	236	245	1	6	7	233	95.10%
13	640 – St. Carolus	13-Aug-18	30-Sep-19	0	225	225	9	3	0	231	102.67%
14	650 – Budi Kemuliaan	2-Aug-18	31-Aug-19	4	225	229	2	5	15	211	92.14%
15	660 – AW Sjahranie	3-Oct-18	30-Sep-19	17	205	222	2	6	3	215	96.85%
16	670 – Zainoel Abidin	9-Apr-19	31-Dec-19	5	121	126	0	4	10	112	88.89%
17	680 – Soedarso	4-Jul-19	31-Dec-19	8	107	115	2	0	8	109	94.78%
18	690 – Abepura	2-Jul-19	30-Jun-20	4	133	137	2	2	7	130	94.89%
19	700 – TC Hilers	8-Jul-19	30-Jun-20	10	170	180	1	1	8	172	95.56%
Total				189	4147	4336	47	52	246	4085	94.21%

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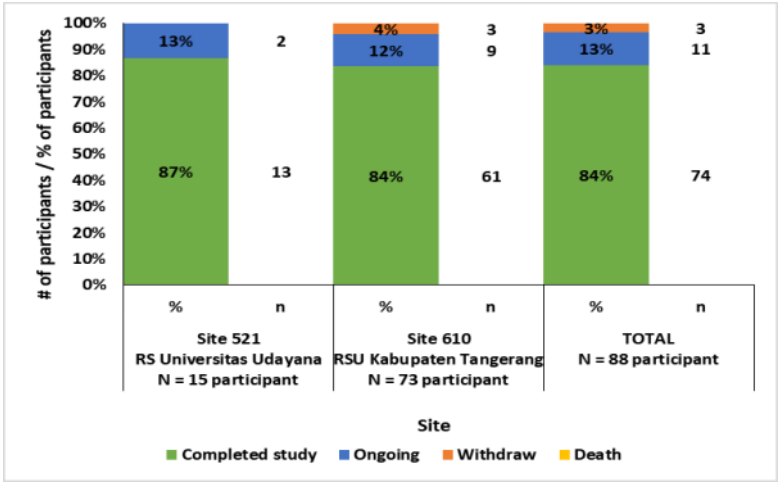
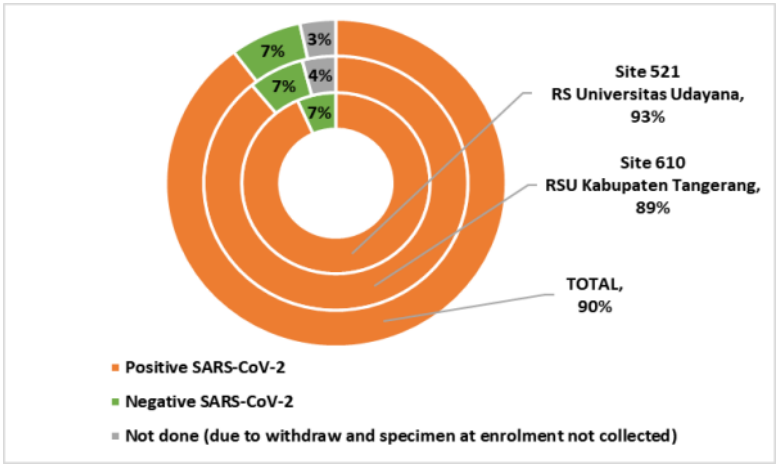
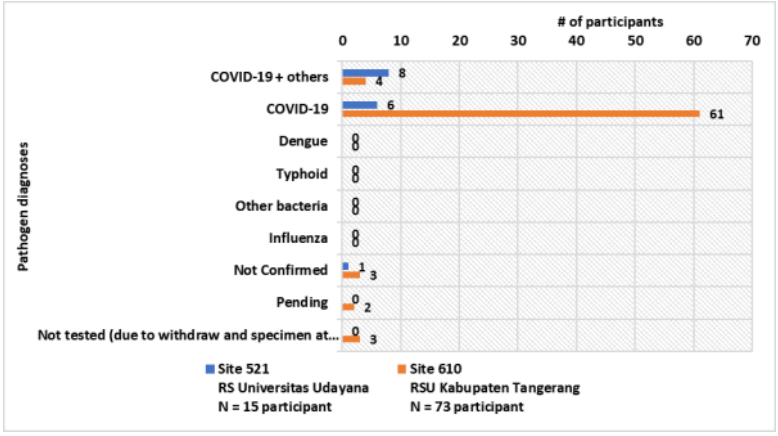
Based on uploaded CRFs as of 20 April 2021, 88 participants enrolled in the ORCHID study, of which 73 participants enrolled in site 610 (RSU Kabupaten Tangerang, Tangerang) and other 15 participants enrolled in site 521 (RS Universitas Udayana, Denpasar). Seventy-two participants completed this study (82 %), with 3 participants who decided to withdraw. Therefore, 13 participants (15 %) are still participating in this study (figure 1).



Up to 20 April 2021, 79 participants (90%) identified as positive SARS-CoV-2, and only 7% identified as negative SARS-CoV-2. In site 610, the number of participants identified as positive SARS-CoV-2 is 65 participants (89%), while in site 521 in 11 participants (93%) identified as positive SARS-CoV-2 (figure 2).



Based on pathogen identification data, at site 521, 8 participants (53%) have been identified with COVID-19 + others and 6 participants (40%) with COVID-19 only. While at site 610, 4 participants (5%) have been identified with COVID-19 + others, and 61 participants' (84%) pathogens have been identified as COVID-19 only. No participant has been identified with a single infection of either Dengue, Typhoid, or Influenza. Two participants are still pending as we are waiting for other lab test results. An examination cannot be performed for the three withdrawn participants (figure 3).



Considering that the number of confirmed COVID-19 subjects is approaching 100 cases, a small group discussion has recently been held to discuss option plans and whether the ORCHID study will continue enrolling the subjects. In the meantime, RS Universitas Indonesia, a new site, is in the process of completing the site assessment report. At the moment, several data available from the on-site assessment report still need to be confirmed, especially concerning the storage of laboratory specimens, before moving to the site preparation visit in May 2021 (Figure 4).

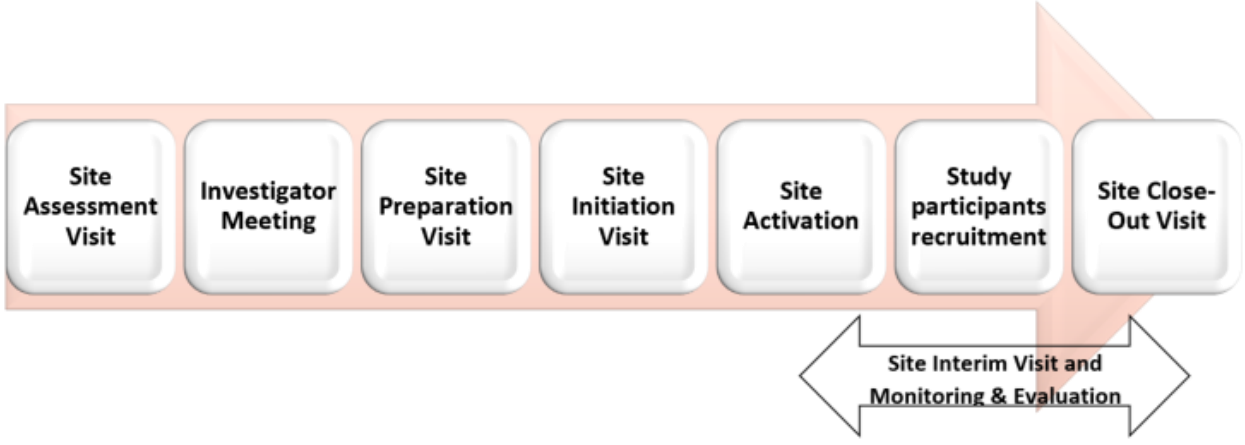


Figure 4. Scheme of site visit scheduled for ORCHID study in RS Universitas Indonesia

INA-RESPOND Newsletter

SARS-COV-2 VARIANTS OF CONCERN VS. CURRENT VACCINES

By: Yan Mardian

As the COVID-19 pandemic continues to spread, SARS-CoV-2 mutation is not unexpected. Across the world, they are now some variant of concern (VOC) that emerge in multiple countries. WHO has defined working definition of VOC by the variant that, through a comparative assessment, has been demonstrated to be associated with an increase in transmissibility or detrimental change in COVID-19 epidemiology, increase in virulence or change in clinical disease presentation, or decrease ineffectiveness of public health and social measures or available diagnostics, vaccines, therapeutics; OR assessed to be a VOC by WHO in consultation with the WHO SARS-CoV-2 Virus Evolution Working Group.

Three VOCs have rapidly become dominant within multiples countries: B.1.1.7 (also known as 20I/501Y.V1 or GRY), B.1.351 (20H/501.V2), and P.1 (20J/501Y.V3). The B.1.1.7 variant (23 mutations with 17 amino acid changes) was first described in the United Kingdom on December 14, 2020; the B.1.351 variant (23 mutations with 17 amino acid changes) was initially reported in South Africa on December 18, 2020; and the P.1 variant (approximately 35 mutations with 17 amino acid changes) was reported in Brazil on January 12, 2021. All three variants have the N501Y mutation, which changes the amino acid asparagine (N) to tyrosine (Y) at position 501 in the receptor-binding domain (RBD) of the spike protein. The 501Y.V2 and P.1 variants both have two additional RBD mutations, K417N/T and E484K. The RBD mutations include the N501Y mutation, which is associated with an increased affinity of SARS-CoV-2 to the ACE2 receptor. In contrast, the E484K and K417N-RBD mutations and mutations in the NTD have been associated with neutralizing antibody escape. By March 30, 2021, the B.1.1.7 variant had been reported in 130 countries, the 501Y.V2 variant in 80, and the P.1 variant in 45 countries.

As currently available vaccines against COVID-19 were first developed during the early pandemic, some concerns arise for

Table 1. *Summary of SARS-CoV-2 VOC, as updated March 30, 2021.*

Pangolin Lineage	B.1.1.7	B.1.351	P.1
Nextstrain Clade	20I/501Y.V1	20H/501.V2	20J/501Y.V3
GISAID Clade	GRY	GH	GR
Alternate names	VOC 202012/01	VOC 202012/02	-
Key Spike Mutation	Δ69/70, Δ144Y, N501Y, A570D, D614G, P681H Some: E484K, S494P	K417N, E484K, N501Y, D614G, L242/A243/L244 deletion	K417N/T, E484K, N501Y, D614G
Key Mutation in common	S106/G107/F108 deletion in Non-Structural Protein 6 (NSP6)		
First Detected	United Kingdom	South Africa	Brazil
Transmission	~50-70% increased transmission	~50% increased transmission	Increased, % unresolved
Lethality	Likely increased severity based on hospitalizations and case fatality rates (~60%)	?	?
Immune evasion	Minimal impact on neutralization by EUA monoclonal antibody therapeutics, convalescent and post-vaccination sera	Moderate impact on neutralization by EUA monoclonal antibody therapeutics, convalescent and post-vaccination sera	Moderate impact on neutralization by EUA monoclonal antibody therapeutics. Reduced neutralization by convalescent and post-vaccination sera
Countries reported	130	80	45

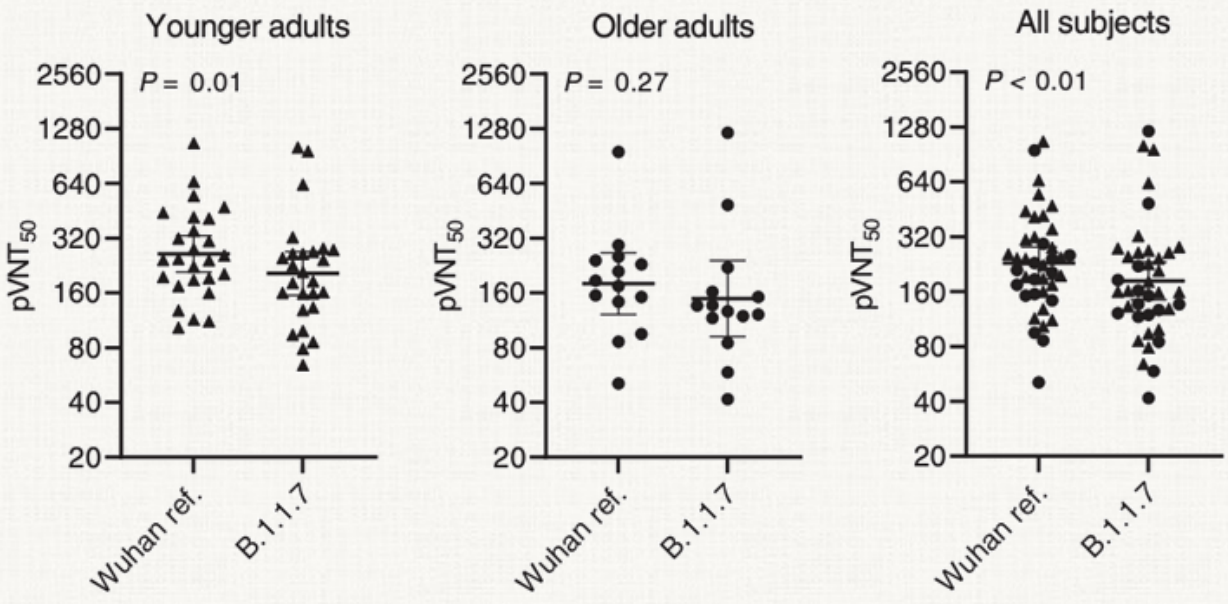


Fig 1. 50% Pseudovirus neutralization titers (pVNT50) of 40 sera from BNT162b2 vaccine recipients against VSV-SARS-CoV-2-S pseudovirus bearing Wuhan reference strain or lineage B.1.1.7 spike protein

reducing the effectiveness of those vaccines against the new variants. Pfizer vaccine (BNT162b2), mRNA-based vaccine platform, has tested their sera participants and showed the immune sera had slightly reduced but overall largely preserved neutralizing titers against the B.1.1.7 lineage pseudovirus. These data indicate that the B.1.1.7 lineage will not escape BNT162b2-mediated protection.

In another study, they performed 50% plaque reduction neutralization testing (PRNT50) using 20 serum samples that had been obtained from 15 participants in the pivotal trial 2 or 4 weeks after the administration of the second dose of 30 µg of BNT162b2 (which occurred 3 weeks after the first immunization). As compared with neutralization of USA-WA1/2020, neutralization of B.1.1.7-spike and P.1-spike viruses was roughly equivalent, and neutralization of B.1.351-spike virus was robust but lower. These findings suggest that mutations that result in amino acid substitutions K417N, E484K, and N501Y in the receptor-binding site have a greater effect on neutralization than the 242–244 deletion affecting the N-terminal domain of the spike protein. Pfizer has said it believes its current vaccine is highly likely to still protect against the South African variant. However, the drugmaker is planning to test a third booster dose of their vaccine as well as a version retooled specifically to combat the variant in order to better understand the immune response.

Other study also showed that entry driven by the S proteins of the B.1.351 and P.1 variants was less susceptible to inhibition by sera/plasma from COVID-19 patients and BNT162b2 - vaccinated individuals as compared to entry driven by WT S protein. Nevertheless, the markedly reduced sensitivity to antibody-mediated neutralization suggests that convalescent and vaccinated individuals might not be fully protected against infection by the B.1.351 and P.1 variants.

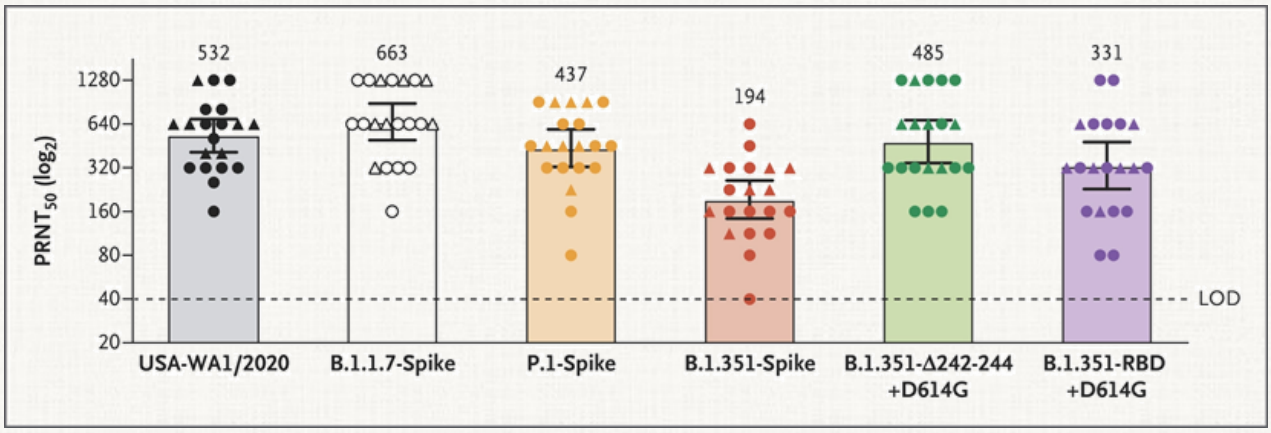


Fig 2. Serum Neutralization of Variant Strains of SARS-CoV-2 after the Second Dose of BNT162b2 Vaccine.

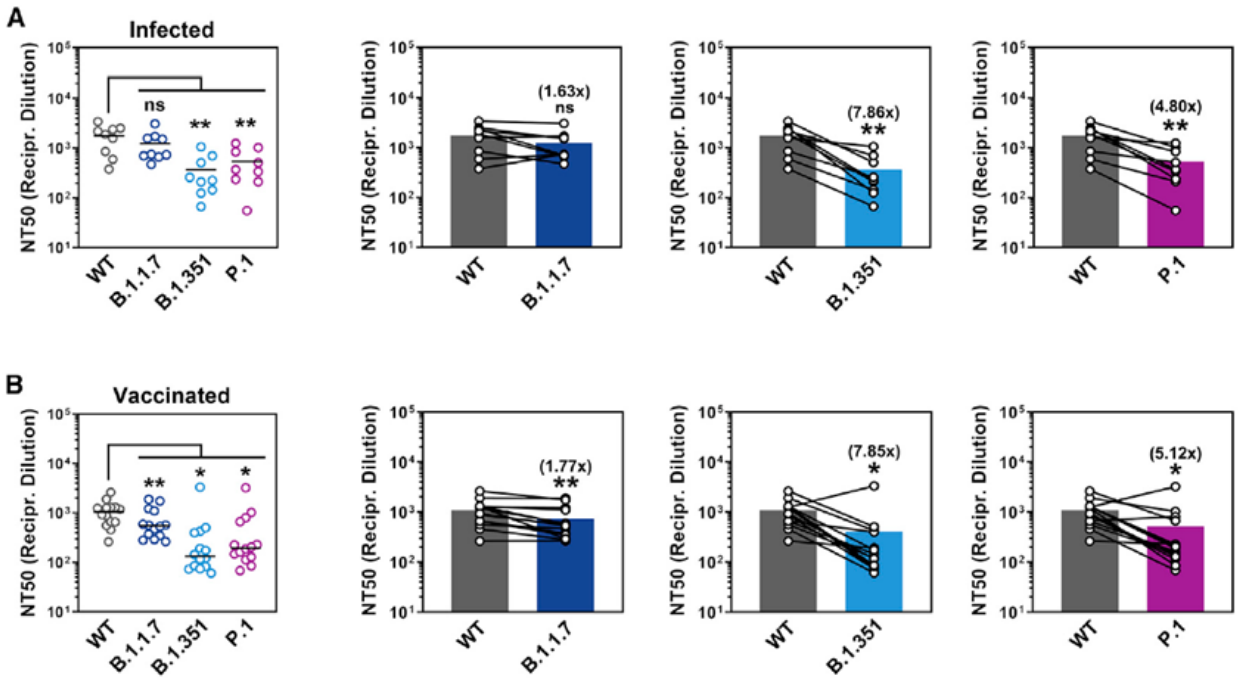


Fig 3. *Entry driven by the S proteins of SARS-CoV-2 variants B.1.351 and P.1 shows reduced neutralization by convalescent plasma and sera from BNT162b2-vaccinated individuals.*

In line with Pfizer, Moderna also assessed its vaccine (mRNA-1273) against the new SARS-CoV-2 variants, using sera from eight Phase 1 clinical trial participants (aged 18-55 years) who received two 100 µg doses of mRNA-1273 in in-vitro neutralization studies. Vaccination with the Moderna COVID-19 Vaccine produced neutralizing titers against all key emerging variants tested, including B.1.1.7 and B.1.351, first identified in the UK and Republic of South Africa, respectively. The study showed no significant impact on neutralizing titers against the B.1.1.7 variant relative to prior variants. A six-fold reduction in neutralizing titers was observed with the B.1.351 variant relative to prior variants. Despite this reduction, neutralizing titer levels with B.1.351 remain above levels expected to be protective.

Another study showed both the full panel of mutations in S and a subset of mutations affecting the receptor-binding domain (RBD) region of the B.1.1.7 variant had no significant effect on neutralization by serum obtained from participants who had received the mRNA-1273 vaccine in the phase 1 trial. In contrast, they observed a decrease in titers of neutralizing antibodies against the P.1 variant, the B.1.427/B.1.429 variant (versions 1 and 2), the B.1.1.7+E484K variant, and the B.1.351 variant as well as a subset

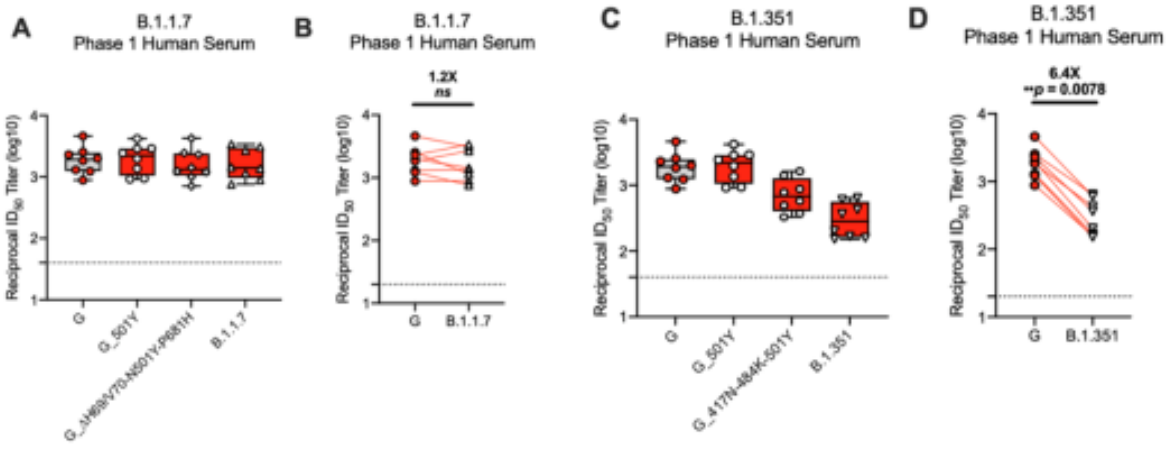


Fig 4. *Neutralization of B.1.1.7 and B.1.351 SARS-CoV-2 pseudoviruses by serum from mRNA-1273-immunized Phase 1 participants*

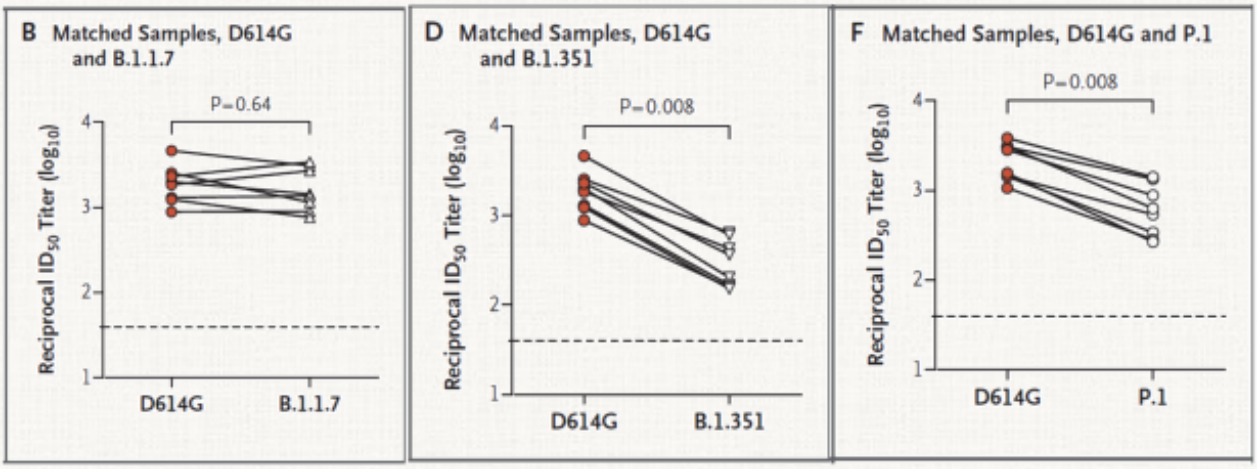


Fig 5. Neutralization of SARS-CoV-2 Pseudoviruses in serum samples obtained from participants who received the mRNA-1273 vaccine

of its mutations in the RBD. We detected reductions by a factor of between 2.3 and 6.4 in titers of neutralizing antibodies against this panel of variants. The largest effect on neutralization, reduction by a factor of 6.4, was measured against the B.1.351 variant.

While initial data confirms that the Moderna COVID-19 Vaccine (mRNA-1273) provides neutralizing activity against variants of concern, out of an abundance of caution, Moderna is pursuing two strategies against these variants, subject to U.S. Food and Drug Administration (FDA) review. First, the company is evaluating booster doses of vaccines to increase neutralizing immunity against the variants of concern. Moderna plans to evaluate three approaches to boosting, including A variant-specific booster candidate, mRNA-1273.351, based on the B.1.351 variant first identified in the Republic of South Africa, at the 50 µg dose level and lower. A multivalent booster candidate, mRNA-1273.211, which combines mRNA-1273, Moderna's authorized vaccine against ancestral strains, and mRNA-1273.351 in a single vaccine at the 50 µg dose level and lower. The third dose of mRNA-1273, the Moderna COVID-19 Vaccine, is a booster at the 50 µg dose level. The company has already begun dosing this cohort with the booster. Second, the company plans to evaluate mRNA-1273.351 and mRNA-1273.211 as a primary vaccination series for those who are seronegative. These candidates will be evaluated in a two-dose series at the 100 µg dose level and lower.

ChAdOx1 nCoV-19, a replication-deficient chimpanzee adenoviral vector containing the sequence of Spike SARS-CoV-2, developed

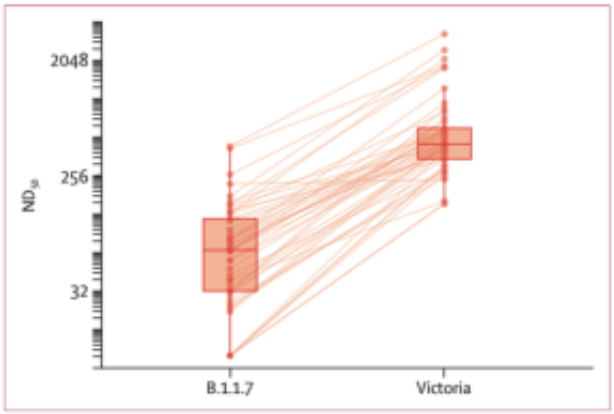


Figure 6: **Live-virus microneutralisation antibody titres of sera against B.1.1.7 and a canonical non-B.1.1.7 strain (Victoria)**
The geometric mean titre is 58 (95% CI 44–77) for B.1.1.7 and 517 (424–631) for Victoria. The geometric mean ratio (Victoria vs B.1.1.7) is 8·9 (95% CI 7·2–11·0). The midlines of the boxes show medians and the outer bounds of the boxes show IQRs. Error bars show the most extreme point within 1·5 × IQR above or below the 75th or 25th percentile. Lines connect samples from the same participant collected at the same trial timepoint (n=49). ND_{50}=titre at which 50% virus neutralisation is achieved.

	Cases*	ChAdOx1 nCoV-19 vaccine (n=4244)	Control vaccine (n=4290)	ChAdOx1 nCoV-19 vaccine efficacy (95% CI)
Primary symptomatic COVID-19				
B.1.1.7	52 (19%)	12	40	70·4% (43·6 to 84·5)
Other variants	95 (35%)	15	80	81·5% (67·9 to 89·4)
No sequence result†	30 (11%)	5	25	80·2% (48·3 to 92·4)
Not sequenced‡	92 (34%)	27	65	59·1% (36·0 to 73·9)
Total cases	269	59	210	72·3% (63·1 to 79·3)
Asymptomatic or unknown infection				
B.1.1.7	19 (9%)	8	11	28·9% (−77·1 to 71·4)
Other variants	34 (16%)	8	26	69·7% (33·0 to 86·3)
No sequence result†	64 (31%)	36	28	−27·0% (−108·1 to 22·5)
Not sequenced‡	92 (44%)	45	47	5·6% (−42·3 to 37·3)
Total cases	209	97	112	14·6% (−12·1 to 34·9)
Any NAAT positive infection§				
B.1.1.7	75 (14%)	21	54	61·7% (36·7 to 76·9)
Other variants	144 (28%)	27	117	77·3% (65·4 to 85·0)
No sequence result†	101 (19%)	44	57	23·7% (−13·0 to 48·5)
Not sequenced‡	200 (38%)	81	119	32·9% (11·0 to 49·5)
Total cases	520	173	347	50·9% (41·0 to 59·0)

Data include SD/SD and LD/SD seronegative efficacy cohorts only. NAAT=nucleic acid amplification test. SD=standard dose. LD=low dose. *Data in this column are n (%) or n. †No viable sequence obtained or unprocessed due to cycle threshold >30. ‡Sample did not enter sequencing pipeline, was destroyed, or sequencing results are yet to be obtained. §Includes primary symptomatic cases, non-primary symptomatic cases (those with other symptoms such as nausea or diarrhoea; not shown separately), asymptomatic cases, and cases for which symptoms were unknown.

Table: **Vaccine efficacy against B.1.1.7 and non-B.1.1.7 variants**

Fig 6. Neutralizing Antibody and ChAdOx1 nCoV-19 vaccine efficacy against B.1.17

by AstraZeneca, also showed reduction efficacy against variants. A pooled analysis of the efficacy of the ChAdOx1 nCoV-19 vaccine in the United Kingdom, Brazil, and South Africa, performed before the emergence of the B.1.351 and P.1 variants, reported an overall vaccine efficacy of 66.7% (95.8% confidence interval [CI], 57.4 to 74.0). Recent analysis of the efficacy of the ChAdOx1 nCoV-19 showed reduced neutralization activity against the B.1.1.7 variant compared with a non-B.1.1.7 variant in vitro, but the vaccine showed efficacy against the B.1.1.7 variant of SARS-CoV-2.

In other trials, two doses of the ChAdOx1 nCoV-19 vaccine showed no efficacy against the B.1.351 variant in preventing mild-to-moderate Covid-19. There were no cases of hospitalization for severe Covid-19 observed in the study. The lack of efficacy against the B.1.351 variant should be considered in the context of the 75% efficacy (95% CI, 8.7 to 95.5) in preventing mild-to-moderate Covid-19 with onset at least 14 days after even a single dose of ChAdOx1 nCov-19 vaccine that was observed before the B.1.351 variant emerged in South Africa. Relative resistance to human neutralizing antibody responses is expected to be a feature of the pandemic coronavirus in the years ahead, as a result of pressure on the virus to select for variants that can transmit despite immunity after natural infection or vaccination. Deliberations on the utility of the ChAdOx1 nCoV-19 vaccine also need to be made in the context of ongoing global spread and community transmission of the B.1.351 variant and the evolution of other SARS-CoV-2 lineages that include similar mutations.

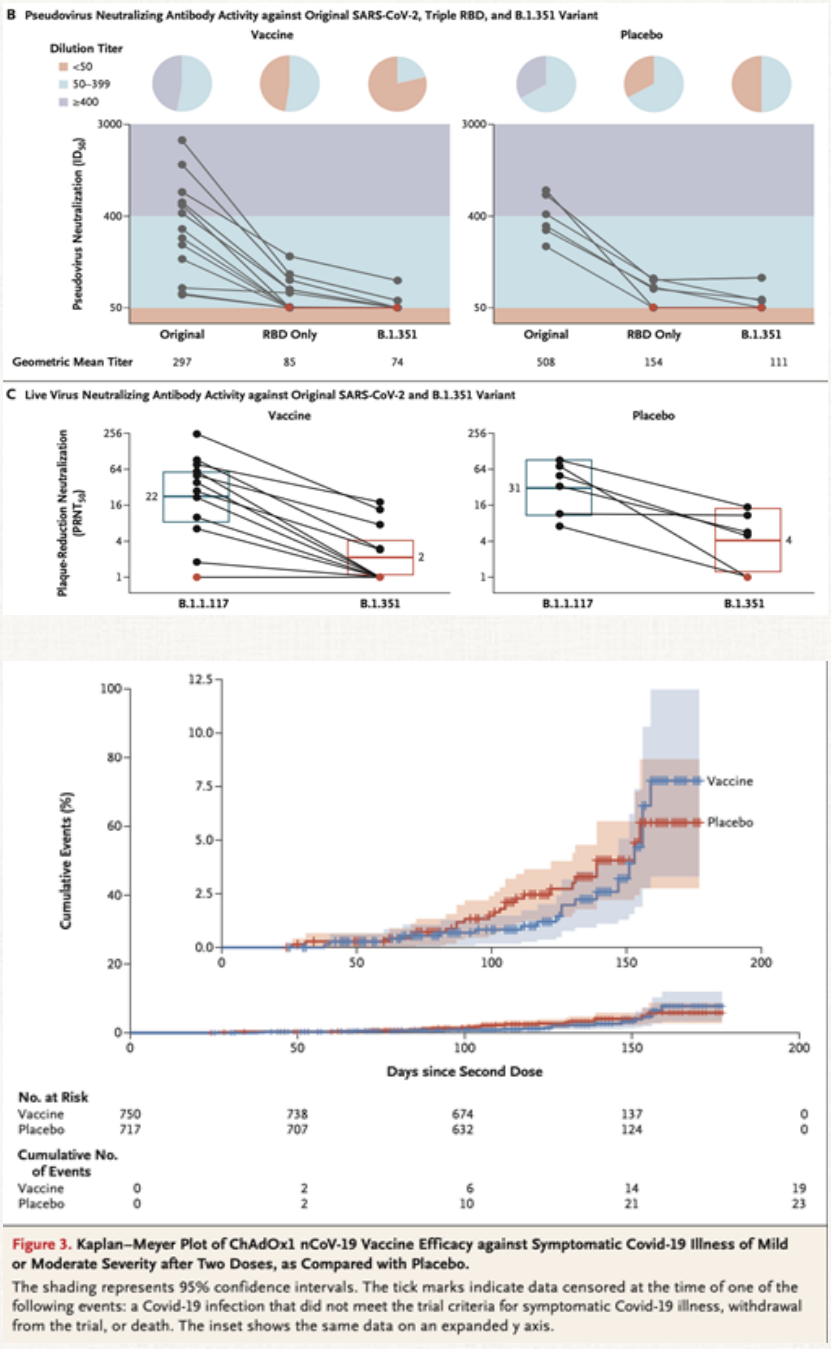


Figure 3. Kaplan–Meyer Plot of ChAdOx1 nCoV-19 Vaccine Efficacy against Symptomatic Covid-19 Illness of Mild or Moderate Severity after Two Doses, as Compared with Placebo.
The shading represents 95% confidence intervals. The tick marks indicate data censored at the time of one of the following events: a Covid-19 infection that did not meet the trial criteria for symptomatic Covid-19 illness, withdrawal from the trial, or death. The inset shows the same data on an expanded y axis.

Fig 7. Neutralizing Antibody and ChAdOx1 nCoV-19 vaccine efficacy against symptomatic COVID-19 Illness of Mild and Moderate Severity after two doses

Another recent multinational study that included South Africa variants evaluated the efficacy of a single dose of the Ad26.COV2.S nonreplicating adenovirus type 26 vaccine (Janssen/ J&J). Interim results showed 66% effective overall at preventing moderate to severe COVID-19, 28 days after vaccination, but the vaccine's efficacy rate dropped from 74.4% in the United States to 52% in South Africa, where 94.5% of viral sequences were from B.1.351 lineage. Subunit vaccine produced by the US biotechnology company Novavax is 96.4 % effective against the original variant of SARS-CoV-2 (UK trial) but also protects against the newer variants B.1.1.7 (86.3%) in the UK phase 3 trial and B.1.351 (48.6%) in South Africa Phase 2b trial.

Analysis of serum samples after vaccination with inactivated virus China vaccines, BBIBP-CorV (Sinopharm) and CoronaVac (Sinovac) showed neutralizing-antibody titers against the B.1.1.7 variant that were

similar to those against the "wild-type" (Wuhan) isolates but were lower against the B.1.351 variant. For the BBIBP-CorV vaccine serum samples, some showed complete or partial loss of neutralization against B.1.351. For the CoronaVac vaccinee serum samples, a marked decrease in the GMTs in the serum neutralization of B.1.1.7 (by a factor of 0.5; 95% CI, 0.3 to 0.7) and B.1.351 (by a factor of 0.3; 95% CI, 0.2 to 0.4) was observed.

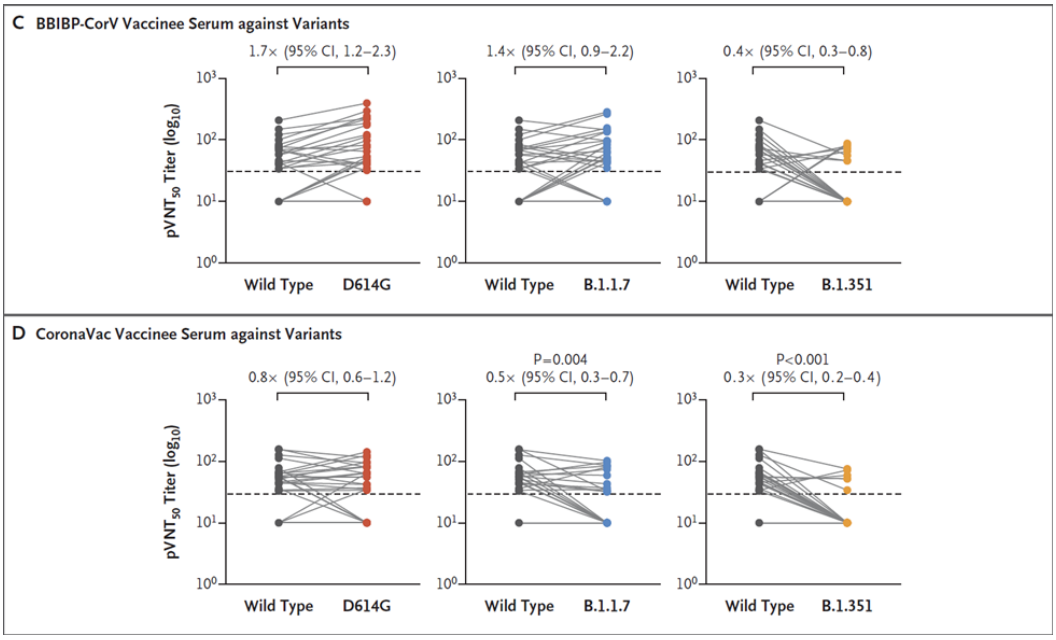


Fig 8. *Neutralizing Antibody of Sinopharm and Sinovac vaccine against variants*

This finding was consistent with the results of other recent studies explained above using other vaccine platforms, highlighting the importance of sustained viral monitoring and evaluation of the protective efficacy of vaccines in areas where variants are circulating.

In summary, studies indicate that the B.1.1.7 variant is, in fact, still can be neutralized by antibodies developed in individuals who have been vaccinated with Pfizer and Moderna mRNA vaccines and still shown high efficacy against severe disease using J&J, Novavax, and Sinopharm vaccines. However, the B.1.351 variant showed a marked reduction of neutralizing antibodies induced by all available vaccines. Summary results on SARS-CoV-2 vaccine trial efficacy and viral neutralization of the B.1.1.7, P.1, and 501Y.V2 Variants, compared with preexisting Variants, are shown below.

Table 1. Summary Results on SARS-CoV-2 Vaccine Trial Efficacy and Viral Neutralization of the B.1.1.7, P.1, and 501Y.V2 Variants, as Compared with Preexisting Variants.*

Vaccine (Company)	Preexisting Variants			Neutralization by Pseudovirion or Live Viral Plaque Assay			Efficacy in Settings with 501Y.V2 Variant
	Sample Size	Efficacy in Preventing Clinical Covid-19	Efficacy in Preventing Severe Covid-19	B.1.1.7 Variant	P.1 Variant	501Y.V2 Variant	
	no.	*% (no. of events with vaccine vs. placebo)*					%
Ad26.COV2.S (Johnson & Johnson)	43,783	66 (NA)	85 (NA)	NA	NA	NA	57†, 85‡
BNT162b2 (Pfizer)	34,922	95 (8 vs. 162)	90 (1 vs. 9)	Decrease by 2×	Decrease by 6.7×	Decrease by ≤6.5×	NA
mRNA-1273 (Moderna)	28,207	94 (11 vs. 185)	100 (0 vs. 30)	Decrease by 1.8×	Decrease by 4.5×	Decrease by ≤8.6×	NA
Sputnik V (Gamaleya)	19,866	92 (16 vs. 62)	100 (0 vs. 20)	NA	NA	NA	NA
AZD1222 (AstraZeneca)	17,177	67 (84 vs. 248)	100 (0 vs. 3)	NA	NA	Decrease by ≤86× to complete immune escape	22§
NVX-CoV2373 (Novavax)	15,000	89 (6 vs. 56)	100 (0 vs. 1)	Decrease by 1.8×	NA	NA	49§
CoronaVac (Sinovac)¶							
Brazil	12,396	51 (NA)	100 (NA)	NA	NA	NA	NA
Turkey	7,371	91 (3 vs. 26)	NA	NA	NA	NA	NA
BBIBP-CorV (Sinopharm)	NA	79 (NA)	NA	NA	NA	Decrease by 1.6×	NA

* Data were available up to March 18, 2021. The definitions of mild, moderate, and severe coronavirus disease 2019 (Covid-19) vary across the vaccine trials. A list of references associated with these vaccines is provided in the Supplementary Appendix, available with the full text of this letter at NEJM.org. NA denotes not available, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.
† Shown is the efficacy of the vaccine, as compared with placebo, against moderate-to-severe Covid-19.
‡ Shown is efficacy of the vaccine, as compared with placebo, against severe Covid-19 and hospitalization.
§ Shown is efficacy of the vaccine, as compared with placebo, against symptomatic Covid-19.
¶ Data are shown separately for the trial sites in Brazil and Turkey.

Table 2. Summary Vaccines Against Variants.

However, it's important to remember that this data is preliminary. Research evaluating neutralization potency against VOC is still needed, emphasizing more laboratory and clinical studies are urgently awaited. Notably, B.1.1.7, B.1.351, and P.1 have now all been identified in multiple countries and are regularly occurring, not to mention that new variants will also continue to emerge. Given the SARS-CoV-2 genome's evolving nature, scientists and drug or vaccine developers should continue to be vigilant for the emergence of new variants or sub-strains of the virus, emphasizes the necessity of genomic surveillance programs that will track SARS-CoV-2 evolution.

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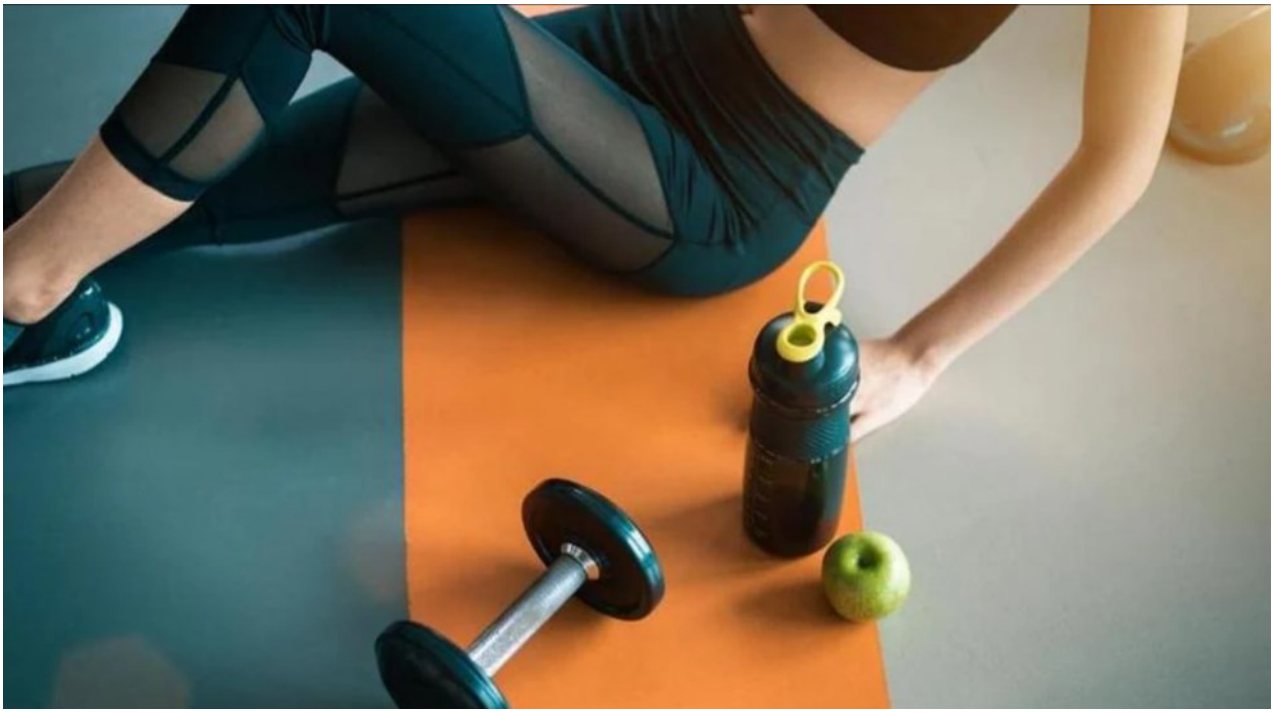
INA-RESPOND Newsletter

FASTING AND EXERCISE DURING RAMADAN TIME

By: Maria Lestari



This year, Ramadan falls from April 12 to May 12 and sees most healthy adults in Muslim communities across the world fasting from sunrise to sunset while reflecting, spending time with family, and celebrating the holy month. This kind of fasting involves daily abstinence from food and water, from sunrise to sunset, which lasts approximately 12 to 17 hours, depending on the season and geographical latitude.1

Ramadan fasting cannot be simply considered as a different diet. The reason is that the pattern and timetable of eating, drinking, and sleeping change in addition to alterations in the food composition during Ramadan. Thus, in Ramadan fasting, in addition to abstention from food and drink, the time of eating, drinking, and sleeping will change, and this may affect athletic performance.2

One day of fasting seems to have no or a little effect on performance. However, thirty consecutive days of fasting may affect various performance factors, including endurance and cognitive functions.3 It is important to look after ourselves and stay healthy during Ramadan, and for people who are particularly into their fitness.

How to Exercise Safely During Ramadan

It is important to be realistic — given your lifestyle changes during Ramadan, your fitness levels likely will too. But that is OK. You can do a few things to make the process a little more palatable and keep yourself safe as you exercise while fasting.

Failing to meet overall nutritional needs or provide specific nutritional support to a session of exercise is likely to impair acute performance and reduce the effectiveness of training or recovery. Muslim exercisers who fast

during Ramadan should use overnight opportunities to consume foods and drinks that can supply the nutrients needed to promote performance, adaptation, and recovery in their sports.4

Which kind of workout is best?

When it comes to exercising during Ramadan, there is no one-size-fits-all approach. However, do prioritize muscular strength because a loss of muscle mass will slow down your metabolism. The goal ought to be to avoid both: losing muscle and a drop in your metabolic rate.5

When it comes to cardio, a light-intensity session is recommended, limited to 30 minutes of slow, steady distance, every other day. Remember, you will be dehydrated, so your body will use your fat storage as an energy source, especially if you do your cardio before iftar. However, the fact that you are depleted means your blood pressure might drop at onset or even after, so do not skip the warm-up and cool-down routines.

Similarly, when you start your resistance training, choose exercises that target the upper body before the lower body to avoid any drop in your blood pressure during or after.

The last fitness aspect to focus on is flexibility to avoid any mobility-related issues you might face, especially when you exercise normally after Ramadan and during the Eid break.

Above all, eating a balanced diet and taking an adequate amount of liquids is necessary to help maintain a healthy exercise routine during the month. Intake of carbohydrates is encouraged during suhoor, which helps to stay energetic. Taking a protein-rich diet after breaking the fast allows the body to rejuvenate.6

The Best Time to Work Out

In a perfect world, you would train an hour or two after consuming plenty of fluid and a small meal of protein, carbs, and a little healthy fat. During the month of Ramadan, that leaves a window either after a small iftar (the "break fast" consumed at sunset) or, if you are extra ambitious, early in the morning after suhoor (the pre-dawn meal).

During the fast, with high temperatures and no liquids from sunrise to sunset, you will compromise your health by pushing yourself too much. It is not recommended to do intensive cardio workouts and heavy weight-training exercises while fasting. It is best to listen to your body.

However, Ramadan fasting did not affect sports performance when the tests were performed in the morning hours or the evening after the iftar meals. Therefore, the optimal time of day for training during Ramadan is the evening, 2-3 hours after breaking the fast.7

Conclusion

Finding an exercise routine that fits around this time can be difficult, and there no one size fits all. Ultimately, it is important to keep things in perspective. Ramadan is not a diet, and although staying healthy is important, it is not the time to be trying to hit PBs (personal best) and get in the best physical shape of your life. The weights room will always be there. And while you can train during Ramadan, there is nothing wrong with taking a break to turn inward.

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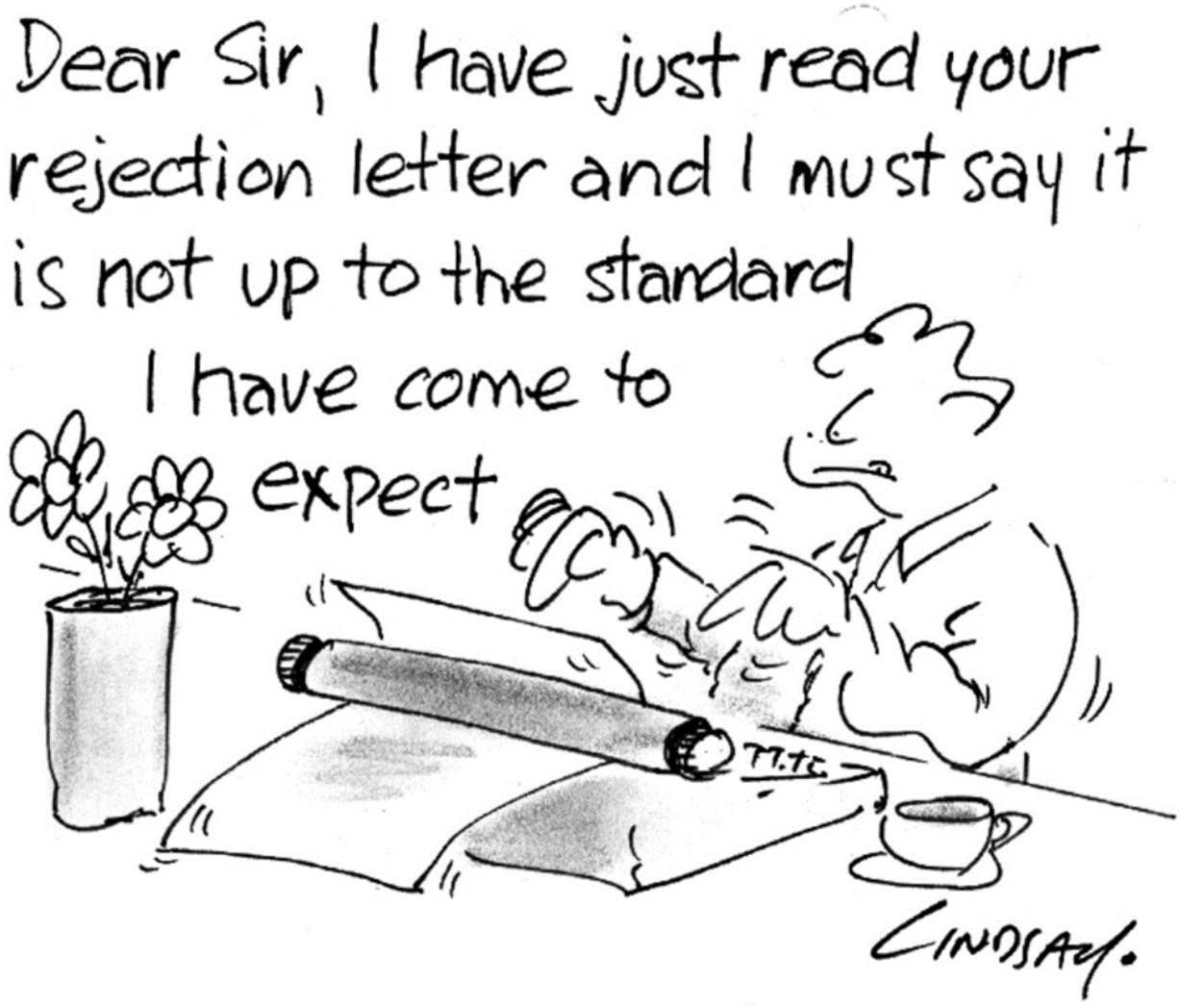
INA-RESPOND Newsletter

RESPONSE TO REVIEWERS – POLITENESS CAN TAKE US A LONG WAY.

By: Aly Diana

COMIC CORNER



Three golden rules of responding to referees' comments: Rule 1. Answer completely; Rule 2. Answer politely; Rule 3. Answer with evidence.

There are three types of editorial decisions about submitted papers: acceptance, rejection (usually immediately by the journal's editor or after peer review), or revision (usually with peer review). Many published papers have been rejected and/or revised several times before being accepted, so please don't get discouraged.

Please do not panic when receiving a "reject after review" decision! Be aware that papers are more often rejected than accepted. Reviewer reports will give us free advice on how to improve our paper. Once you have received the decision, please read it, sleep on it, and read it again, reflecting on the reasons for rejection.

Share the rejection decision with our co-authors, and use the opportunity to further strengthen your manuscript before submitting it to a different journal. Do not leave it too long. Motivate ourselves to start the next submission as soon as possible. Be as careful with a new submission of our paper as with the first.

When receiving a "revise and resubmit" decision, read the report carefully and let it sink in before writing the response. Copy/paste all comments into a new document and respond to each comment according to the following structure: (1) author's response: briefly respond to the criticism and (2) changes to the paper: state whether and where in the paper we have made revisions. When we make changes to the text or figures, quote the changes directly in the response. We should refer to the specific line number where the changes were applied and be sure to specify whether we refer to the line numbers from the original or the revised manuscript. Mark the text changed since the previous version in our revised paper using the track changes.

Some comments can be addressed in the author's response without making changes to the paper, particularly when there were no specific suggestions for revision by the reviewer. In any case, reviewers reading our response and the revised paper should get the impression that we have taken their comments seriously and that we have done our best to improve the paper accordingly. A self-contained response letter makes it easier for the reviewer to understand exactly what we did without flipping back and forth between our manuscript and the response. Furthermore, by making our response self-contained, you reduce the likelihood that the reviewer will read the full manuscript and find new things to complain about.

Always be respectful toward the reviewers in our response to their comments. Add a word of thanks to each reviewer for taking the time to suggest improvements and try to adhere to as many suggestions for revision as you can agree with. Even if we are convinced that the reviewer lacks intellectual capacity, it is certainly not in our interest to convey this impression to the reviewer. Keep in mind that if the reviewer failed to understand something, the fault likely lies, at least in part, with us for not making the point clear enough. If the reviewer does not seem to be an expert in the area, remember that this level of expertise (or lack thereof) may represent many readers of the journal. Our goal is to make the work clear and accessible to all readers, not just to experts. We can, however, also respectfully disagree with a reviewer's comment. Provide solid arguments to support our point of view, including references to evidence from our own data or previously published work.

In general, we should avoid giving the impression that we couldn't be bothered to carry out the additional experiments or analyses that the reviewer asks for. Even in cases in which we believe the reviewer has requested an analysis that we don't find informative or is otherwise flawed, we will often be in a stronger position if we do what the reviewer asked, report the results in our response, and then explain why we believe the results do not belong in your manuscript. Before resubmitting to the journal, circulate our responses and the revised paper among the co-authors, incorporate their feedback, and get their approval on the new version. If we never give up, in the end, we will find that hoped-for e-mail in our in-box headed "accepted for publication." Cherish that moment and be sure to celebrate it!

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