INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

May 2021

Sports & Lifestyle
Boost Your Vaccine with Exercise!

Science Corner
Update on SARS-CoV-2 genomic variants

Comic Corner
Policy Brief, Policy Bridge

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

2021

INA-RESPOND newsletter

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FEATURES

INA-RESPOND Newsletter

TRIPOD & PROACTIVE Study Updates

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

STUDY UPDATES

INA102

Per 06 May 2021, all of the participants in the TRIPOD study have a study completed from 490 enrolled participants. Two hundred and fifty-four participants have completed the study, while 236 participants are terminated early (including death). From the uploaded CRFs, all participants from sites 520, 550, 560, 570, 580, 590, and 600 have been completed the study. The Source Document Worksheet has completed upload from sites 520, 550, 560, 570, 590, and 600.

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 has been conducted on 29-30 March 2021 and 2-17 April 2021.

The Site Close-out Visit (SCV) has been 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 study documents from these sites will be archived in the IndoArsip for long-term archival at least 5 years after the study is closed.

Regarding the closure at site 520, the INA-RESPOND secretariat has announced an official letter and a final report on site closure to the hospital director and the local ethics commission for sites 570, 590, and 560 will be proposed later.

The TRIPOD isolate has been sent to Central Laboratory in Padjajaran University Bandung on 12 April 2021 for doing the subculture. Subculture will be prepared for several tests regarding TB, including TB strain examinations which is one of the TRIPOD secondary objectives.

Per protocol, there are 8 type of specimens collected on TRIPOD study for future used. Status for Repository specimens is provided in figure 4.

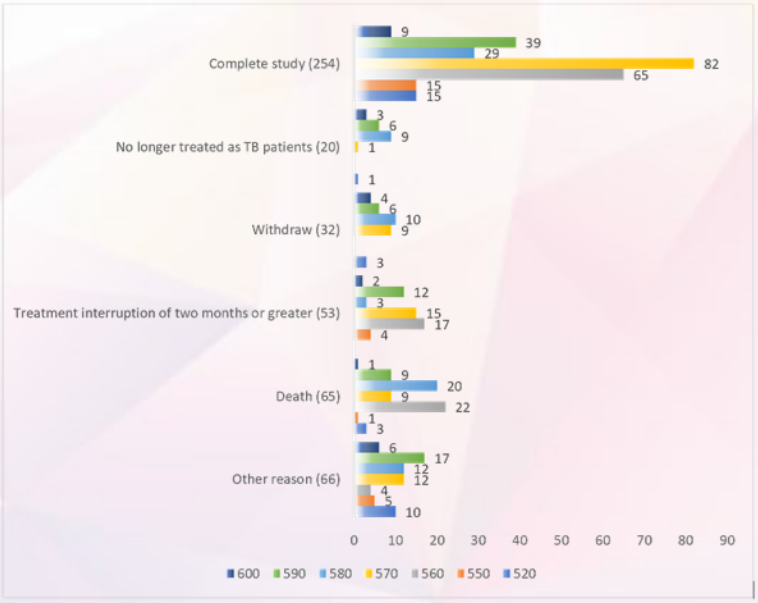

Figure 1.Participant status per site based on uploaded CRF per 06 May 2021.

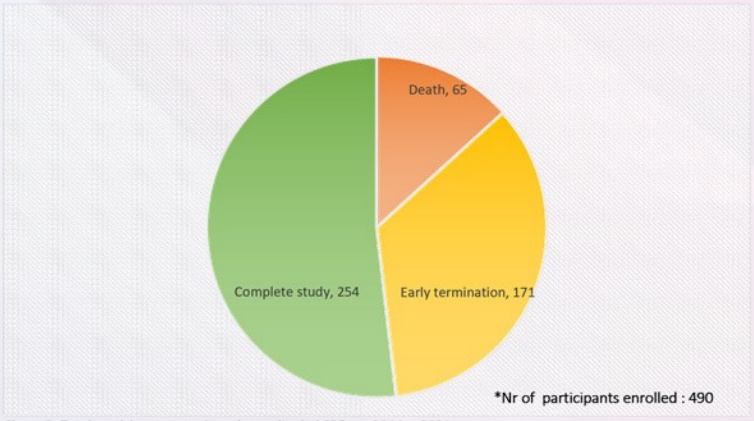

Figure 2. Total participant status based on uploaded CRF per 06 May 2021.

Site	Site Closed Out Visit	Awaiting Items
520 (n=32)	Done, 30 November – 1 December 2020	Sending the study documents to Indo Arsip
550 (n=25)	Planned, 22-23 June 2021	SCV preparation but not limited to QA Process by DM, File Review by CRSS and Specimen Management Review by CRA
560 (n=108)	Done, 20-21 April 2021	Sending the study documents to INA RESPOND DST result for 1 subject
570 (n=128)	Done, 15-16 December 2020	Sending the study documents to INA RESPOND and Indo Arsip
580 (n=83)	Planned, 24-25 Augusts 2021	SCV preparation but not limited to QA Process by DM, File Review by CRSS and Specimen Management Review by CRA
590 (n=89)	Done, 19-20 January 2021	Sending the study documents to Indo Arsip
600 (n=25)	Planned, 20-21 July 2021	SCV preparation but not limited to QA Process by DM, File Review by CRSS and Specimen Management Review by CRA

Site	Specimen Type	Whole blood (EDTA) - DNA	Whole blood (Heparin) - PBMCs	Whole blood (Heparin) – Plasma	Whole blood (PAXgene) - RNA	Urine	Saliva	Sputum	MTB Isolate
520 (n=32)	**BL (32)**	90	22	91	27	125	62	19	36
	M1 (24)	NA	18	64	21	99	NA	16	12
	M2 (24)	NA	22	68	24	93	NA	11	0
	EOT (15)	NA	28	45	15	60	30	2	0
560 (n=108)	**BL (108)**	382	204	328	102	440	216	131	272
	M1 (95)	NA	188	285	94	381	NA	107	60
	M2 (87)	NA	172	261	86	348	NA	91	20
	EOT (73)	NA	142	219	73	292	146	75	19
570 (n=128)	**BL (128)**	438	177	380	121	519	254	119	192
	M1 (104)	NA	162	311	103	416	NA	43	92
	M2 (97)	NA	162	294	98	392	NA	22	38
	EOT (80)	NA	162	243	81	320	160	4	12
580 (n=83)	**BL (83)**	235	130	210	67	308	147	26	42
	M1 (44)	NA	70	102	38	156	NA	18	6
	M2 (38)	NA	54	81	36	148	NA	16	0
	EOT (29)	NA	50	71	27	124	61	8	0
590 (n=89)	**BL (89)**	340	170	255	84	344	147	78	55
	M1 (59)	NA	98	147	49	196	NA	17	8
	M2 (56)	NA	80	120	41	164	NA	8	0
	EOT (40)	NA	46	72	24	96	46	9	0
600 (n=25)	**BL (25)**	100	50	75	25	100	50	50	30
	M1 (13)	NA	26	39	13	52	NA	26	4
	M2 (11)	NA	22	33	11	44	NA	22	4
	EOT (9)	NA	20	30	10	40	20	20	0
550 (n=25)	**BL (25)**	95	48	72	24	100	51	10	27
	M1 (20)	NA	36	54	19	68	NA	7	7
	M2 (20)	NA	36	54	17	72	NA	6	4
	EOT (15)	NA	26	39	13	52	25	0	2

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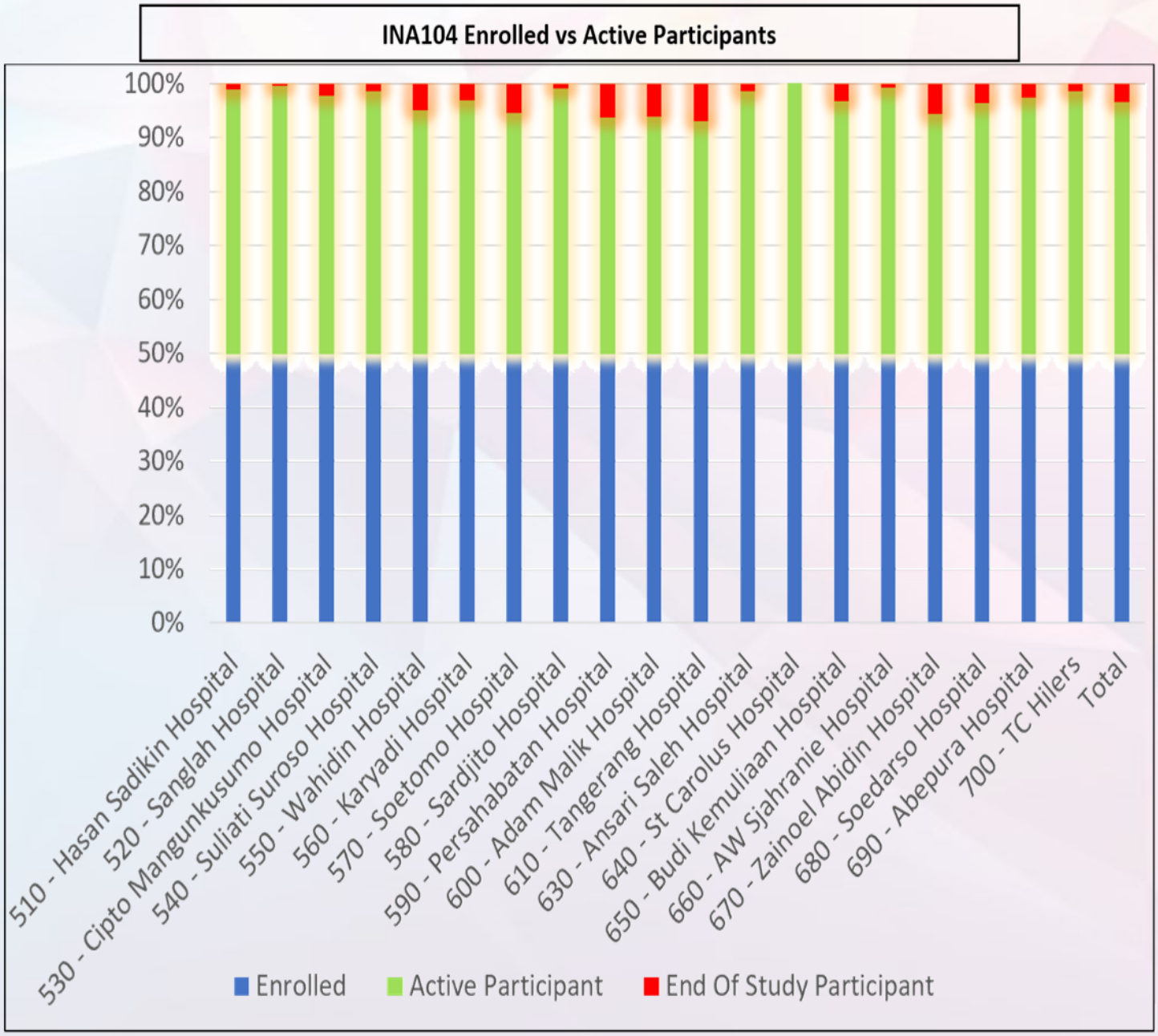
According to the data per 11 May 2021, from 4,336 subject enrolled, 285 subjects are End of Study due to these reasons: 176 subjects' death, 23 subjects move away to the city which site PROACTIVE is not available, 25 subjects withdrew, 5 subjects with negative HIV test result, and 56 subjects that have completed the last Follow Up Month 36 which is 1 subject at Site 530 (Cipto Mangunkusumo Hospital), 10 subjects at Site 550 (Wahidin Sudirohusodo Hospital), 1 subject from Site 570 (Soetomo Hospital), 20 subjects at Site 600 (Adam Malik Hospital, Medan) and 24 subjects at Site 610 (Tangerang Hospital). Below is the Chart of Enrolled and Active Participants by Sites:

Meanwhile, Onsite SMV (Site Monitoring Visit) was conducted to Site 570 (Soetomo Hospital) on May 3-5 and remote SMV conducted to Site 610 (Tangerang Hospital) on May 6-7.



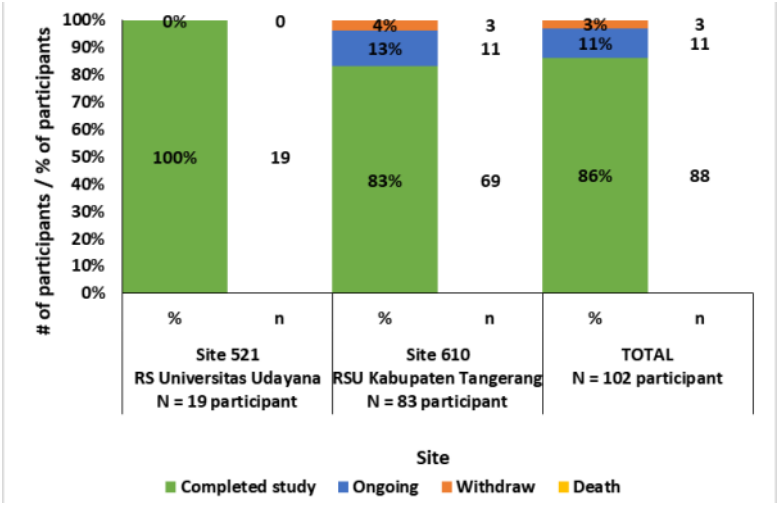
INA107

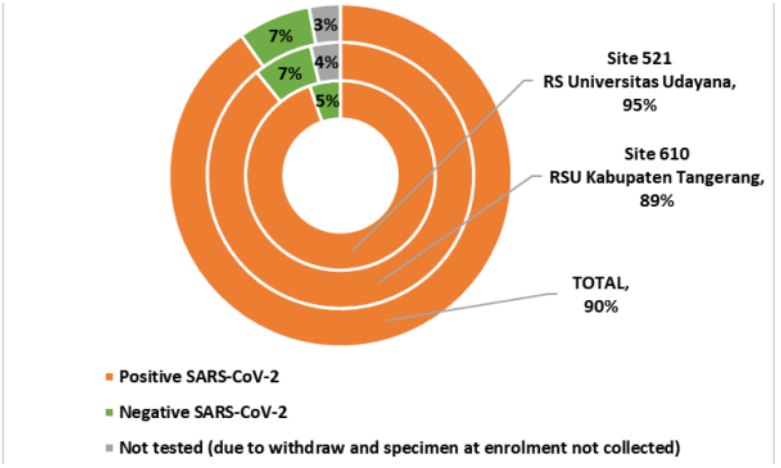
Based on uploaded CRFs as of 10 May 2021, 102 participants enrolled in the ORCHID study, of which 83 participants enrolled at site 610 (RSU Kabupaten Tangerang, Tangerang) and 19 participants enrolled at site 521 (RS Universitas Udayana, Denpasar). Seventy-two participants completed this study (82 %), with 3 participants who decided to withdraw. Therefore, 13 participants (15 %) are still participating in this study (figure 1).

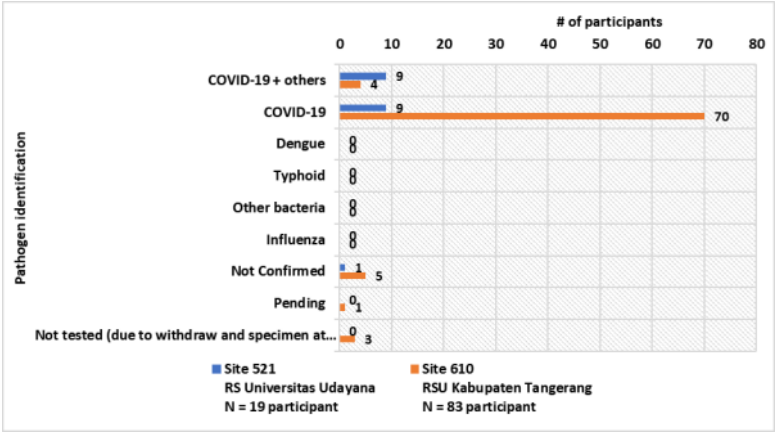
Up to 10 May 2021, 92 participants (90%) identified as positive SARS-CoV-2, and only 7% identified as negative SARS-CoV-2. At site 610, the number of participants identified as positive SARS-CoV-2 is 74 participants (89%), while at site 521, there were 18 participants (95%) identified as positive SARS-CoV-2 (figure 2).

Based on pathogen identification data, at site 521, 9 participants (53%) have been identified with COVID-19 + others and 9 participants (47%) 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 visit report and equipment for study preparation. If the site can complete the necessary requirement and can be activated next month (in June) then they will be included as the 3rd study site.







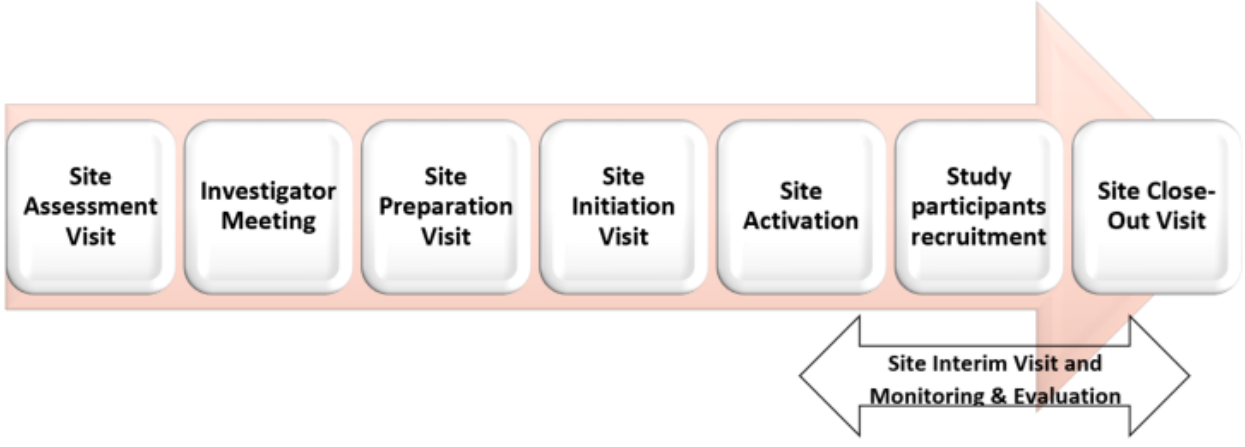


Figure 4. Scheme of site visit scheduled for ORCHID study in RS Universitas Indonesia

INA-RESPOND Newsletter

ALLELIC DIVERSITY OF MEROZOITE SURFACE PROTEIN GENES (MSP1 AND MSP2) AND CLINICAL MANIFESTATIONS OF PLASMODIUM FALCIPARUM MALARIA CASES IN ACEH, INDONESIA

By: Kurnia Fitri Jamil1*, Nandha Rizki Pratama2, Sylvia Sance Marantina2, Harapan Harapan3, Muhammad Riza Kurniawan4, Tjut Mariam Zanaria5, Jontari Hutagalung6, Ismail Ekoprayitno Rozi2, Puji Budi Setia Asih2, Supargiyono7^ and Din Syafruddin2,8

Abstract

Background: The malaria control program in Indonesia has successfully brought down malaria incidence in many parts of Indonesia, including Aceh Province. Clinical manifestation of reported malaria cases in Aceh varied widely from asymptomatic, mild uncomplicated to severe and fatal complications. The present study aims to explore the allelic diversity of merozoite surface protein 1 gene (msp1) and msp2 among the Plasmodium falciparum isolates in Aceh Province and to determine their potential correlation with the severity of malaria clinical manifestation.

Criteria for severe malaria

Severe falciparum malaria is defined as one or more of the following [11], occurring in the absence of an identified alternative cause and in the presence of P. falciparum asexual parasitaemia: (a) impaired consciousness, (b) prostration, (c) multiple convulsions, (d) hypoglycemia, (e) renal impairment, (f) jaundice, (g), pulmonary oedema and (h) significant bleeding, such as haematemesis or melaena.

Fig. 1 Study sites in Aceh; Kota Banda Aceh, Sabang, Kota Lhokseumawe, Aceh Besar, Aceh Barat Daya, Nagan Raya, Aceh Barat, Aceh Jaya, Aceh Utara, Pidie Jaya, and Pidie

Methods:

Ethical statement

This study has been approved by the Medical and Health Research Ethics Committee, Faculty of Medicine Gajah Mada University, with reference No: KE/FK/173/EC. All subjects were asked for informed consent prior to participation. Screening of over 500 malaria cases admitted to the hospitals in 11 districts hospital within Aceh Province during 2013–2015 identified 90 cases of P. falciparum mono-infection without any co-morbidity. The subjects were clinically phenotyped, and parasite DNA was extracted and polymerase chain reaction (PCR) amplified for the msp1 and msp2 allelic subfamilies.

DNA extraction and polymerase chain reaction

The parasite DNA was extracted from the filter paper using Chelex-100 ion exchanger method as described previously [13]. The DNA extract was used as the template for the nested-1 PCR for determining species of the parasite [14], and only cases with monoinfection with P. falciparum will be enrolled. All enrolled subjects will be PCR amplified using oligos that target the parasite msp1 and msp2 genes with a total of 25 µl volume was used for all reactions [15].

Multiplicity of infection (MOI)

MOIs were calculated by dividing the total number of distinct msp1 and msp2 genotypes by the number of positive samples for each marker. The mean MOI was calculated by dividing the total number of alleles detected in both msp1 and msp2 by the total number of positive samples for both markers. Samples were considered single infected when harboring only one allele at each of the genotyped loci. Multiclonal infections were defined as infections with more than one allele in at least one locus.

Results: The study subject's recruitment flowchart and the procedures applied to subjects is shown in Fig. 2. Of the total 500 subjects admitted to the hospitals with fever, 176 subjects (52 males and 38 females) were found positive by microscopy and

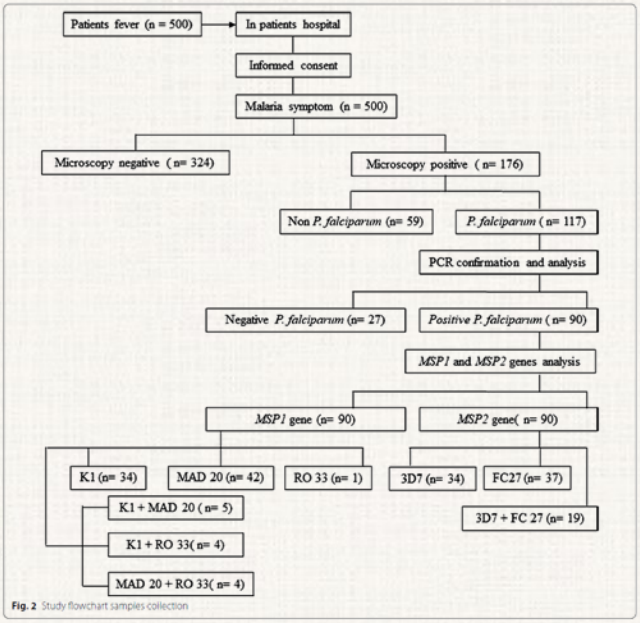


Fig. 2 Study flowchart samples collection

117 of which by P. falciparum. Further validation by PCR revealed 90 subjects with P. falciparum mono infection. Among the 90 study subjects, 57.7% of them were males and 42.3% were females with most subjects 46.7% aged between 21 and 30 years old (Table 1).

Analysis of clinical manifestation revealed that fever-chill is the most frequent symptom. Based on WHO criteria showed 19 cases were classified as severe and 71 as mild malaria. The clinical manifestation, origin, and laboratory profiles of each subject are shown in Table 2. The commonly observed symptoms and signs include fever with chill (100%), dyspnoea (75.6%), and spleen enlargement (87.8%). Severe signs such as shock, convulsion, and conscious disturbance were observed in few cases. Laboratory assays revealed anaemia in 36.8% of the subjects, abnormalities in the values of the liver (63%) and kidney (95.6%) function, and haemoglobinuria (20%). Of the 90 subjects examined 92% had a parasite density of 10,000 parasites per microlitre blood, and the remaining 8% had a parasite density of less than 10,000/µl blood. The parasite density of the subjects ranged from 5000 to 15,000 parasites per microlitre blood. Based on WHO classification [12], 19 (21%) subjects were classified as severe malaria whereas the remaining 71 (79%) subjects were mild, uncomplicated malaria.

Table 1 Characteristics of study subjects *Plasmodium falciparum* malaria cases

Variable	Overall
Number of patients enrolled	90
Age (year)	
Mean	33 (36%)
Range	19–63
< 20	6 (6.66%)
21–30	42 (46.7%)
31–40	23 (25.55%)
41–50	12 (13.23%)
51–60	5 (5.55%)
> 60	2 (2.22%)
Gender	
Male [n (%)]	52 (58%)
Female [n (%)]	38 (42%)
Body temperature [℃, mean (SD)]	
< 37.5 ℃	0
≥ 37.5 ℃	90 (100%)
Parasite density (/ul)	
Range	5000–15.000
Mean	12.500
> 10.000	82 (91%)
≤ 10.000	8 (9%)

Analysis of msp1 gene revealed the presence of K1 allele subfamily in 34 subjects, MAD20 in 42 subjects, RO33 in 1 subject, and mixed allelic of K1 + MAD20 in 5 subjects, K1 + RO33 in 4 subjects, and MAD20 + RO33 in 4 subjects. Analysis of msp2 gene revealed 34 subjects carried the FC27 allelic subfamily, 37 subjects carried the 3D7, and 19 subjects carried the mixed

Table 2 Clinical manifestation and laboratory profiles in Aceh Province

Profile	Symptoms and Signs	Total
Physical examination	Fever (≥ 37.5 ℃)	90 (100*)
	Dyspnea	68 (75.6)
	Splenomegaly	79 (87.8)
	Convulsion	2 (2.2)
	Conscious disturbance	4 (4.4)
	Shock	3 (3.3)
Laboratory parameters	Anemia	33 (36.7)
	Abnormality in the values of liver function	57 (63.3)
	Abnormality in the values of kidney function	86 (95.6)
	Haemoglobinuria	18 (20)

(*) = percentage (%)

FC27 + 3D7. Analysis of multiplicity of infection revealed that msp1 alleles are slightly higher than msp2 with the mean of MOI, which were 2.69 and 2.27, respectively. Statistical analysis to determine the association between each clinical manifestation and msp1 and msp2 alleles revealed that liver function abnormal value was associated with the msp2 mixed alleles (odds ratio (OR):0.13; 95%CI: 0.03–0.53). Mixed msp1 of K1 + RO33 was associated with severe malaria (OR: 28.50; 95%CI: 1.59–1532.30).

Conclusion

Allelic subfamilies analysis of the msp1 and msp2 genes among the hospitalized uncomplicated and severe malaria cases in Aceh have been analyzed. Association between liver function abnormal value with the mixed allelic type of msp2 was observed. Mixed allelic infection of msp1 K1 and RO33 is strongly associated with severe malaria. This study has several limitations, such as analyzing symptomatic malaria cases and only a few severe cases. Further study to explore more subjects in different geographic settings and different clinical manifestations is recommended.

From left to right:
Prof. Dr. Din Syafruddin, Ph.D.;
Dr. dr. Kurnia Fitri Jamil, M.Kes, SpPD, KPTI, FINASIM.;
Dr.Puji BS Asih, M. Sc;
Dr. Jontari Hutagalung, MPH.

Table 3 Allelic frequency of the *msp1* and *msp2* genes in Aceh

Gene	Allele sub-family	Number	(%)	Amplicon	Allele
msp1	K1	34	37.7	160–350*	3
	MAD20	42	46.7	160–500	5
	RO33	1	1.1	130–220	2
	K1 + MAD20	5	5.6	–	–
	K1 + RO33	4	4.4	–	–
	MAD20 + RO33	4	4.4	–	–
msp2	FC27	37	41.1	250–530	4
	3D7	34	37.7	100–450	3
	FC27 + 3D7	19	21.2	–	–

*Base pairs

Gene	Allele	Severe		Mild		p-value	OR	CI95%
		n	%	n	%			
msp1	K1	7	36.8	27	38	0.17	2.46	0.55–12.50
	MAD20	4	21	38	53.6	–	–	–
	RO33	0	0	1	1.4	–	–	–
	K1 + MAD20	1	5.4	4	5.6	0.47	2.37	0.03–33.59
	K1 + RO33	3	15.8	1	1.4	0.00	28.50	1.59–15.32
	MAD20 + RO33	4	21	0	0	–	–	–
msp2	3D7	7	36.8	30	42.3	–	–	–
	FC27	11	57.9	23	32.4	0.19	2.04	0.6–7.22
	FC27 + 3D7	1	5.3	18	25.3	0.16	0.23	0.01–2.15

Table 4. Association of malaria severity with the msp1 and msp2 alleles

INA-RESPOND Newsletter

UPDATE ON SARS-COV-2 GENOMIC VARIANTS

By: Katy Shaw-Saliba

FROM OUR PARTNER

Introduction

An incredible 1.6 million+ SARS-CoV-2 genomes have been deposited in the GISAID database globally. This effort is paramount as the pandemic continues and vaccines are rolled out to track changes in the genome and monitor for potential SARS-CoV-2 variants.

In the January edition of the newsletter, SARS-CoV-2 variants were introduced and the different phenotypic data of the three major VOCs (B.1.1.7 from the UK, B.1.351 from South Africa, and P.1 from Brazil) were outlined.

Since the January edition of the newsletter, the WHO 1 and a US Government SARS-CoV-2 Interagency Government (SIG) Working Group (which includes NIH)2 have published criteria on determining if a variant is a Variant of Concern (VOC) or a Variant of Interest (VOI). The major difference between a VOC and a VOI is a VOC has documented evidence of any of the following: increased transmission, impact on diagnostics, increased disease severity, impact on therapeutics, and/or impact on immunity AND is associated with increasing case numbers. A VOI on the other hand is associated with increasing case numbers and mutations that are suspected to impact any of the criteria outlined above2.

Since January, new information on the three VOCs has been published and communicated through preprint and press. An additional VOC has also been identified in the US: CAL.20C/B.1.427/B.1.4293-5 and other VOIs have been described globally6-9. A summary is provided in **Table 1**.

Variant of Concern (VOC)	B.1.1.7 (20I/501Y.V1)	B.1.351 (20H/501Y.V2)	P.1 (20J/501Y.V3)	B.1.427/B.1.429* (CAL.20C)
Location of origin	UK	South Africa	Brazil	United States
Diagnostic evasion	Yes[10]	No	No	No
Viral load increase **Patient specimens[&]** **Animal models**	 Yes[10-15] Yes[16]	 Yes[13] Yes[17]	 Potentially[13,18] Yes[17]	 Yes[4] nd
Increased Transmissibility	Yes (35-75% increase) [19-22]	Yes (50% increase)[23]	Yes (1.4-2.7 times higher) [18,24]	Yes (20% increase)[4]
Disease severity	Increased mortality[19,25]	nd	[#]Increased mortality in younger adults[17,26,27]	Potentially[4]
Impact on monoclonal antibody therapy[x] Bamlanivimab + Etesevimab Casirivimab + Imdevimab	 No change[28] No change[28]	 Significantly reduced activity[28] Slight decrease casirivimab only[28]	 Significantly reduced activity[28] Slight decrease casirivimab only[29]	 Significantly reduced bamlanivimab only[30] No data

Table 1. Updated information on VOCs.
Citations shown as superscript numbers
*The B.1.427 and B.1.429 are two different viral genotypes but largely have been characterized together based on common mutations and therefore are presented here as one variant.
[&]Using Ct value on RT-PCR as a proxy
[#] Collapse of the health system may contribute
nd = no data (yet)
[x]Monoclonal antibody therapy (mAb): two combination mAb therapies have received Emergency Use Authorization (EUA) from the US Food and Drug Administration (FDA) for treatment of mild to moderate COVID-19 in adults and pediatric patients (Bamlanivimab + Etesevimab from Eili Lilly & REGEN-COV2: Casirivimab + Imdevimab from Regeneron)[31]. Others are in clinical trials see refs[28,32,33]

With the rollout of vaccines, the focus of this month's update will be on the available information on the impact of the VOCs on immunity from natural infection (convalescent plasma) or vaccines.

Spike mutations in the VOCs

To understand the impact of VOCs on immunity (natural or vaccine), it's helpful to compare the mutations in the Spike across the VOCs (Table 2). While the VOCs also contain other mutations, Spike is essential for the interaction with the host ACE2 receptor and is the major target of neutralizing antibodies (antibodies that block the ability of the virus to interact with the host).

VOC	Spike mutations/deletions
B.1.1.7 (20I/501Y.V1)	Δ69–70 HV, Δ144 Y, N501Y, A570D, D614G, P681H, T761I, S982A, D1118H
B.1.351 (20H/501Y.V2)	L18F, D80A, D215G, ΔL242-L244, R246I, K417N, E484K, N501Y, D614G, A701V
P.1 (20J/501Y.V3)	L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I
B.1.427 B.1.429 (CAL.20C)	L452R, D614G S13I, W152C, L452R, D614G

Table 2. Spike mutations (substitutions) in the COVs

Impact on convalescent plasma (proxy for impact on pre-existing immunity)

Monitoring the impact of variants on the neutralizing activity of convalescent plasma can serve as a in direct means to measure the impact on pre-existing immunity from natural infection. While correlates of protection (the elements of the immune system that are essential for protection from infection/reinfection) are not fully described, neutralizing antibody titers could be one measure. Neutralizing titers can be compared to other variants or the wildtype D614G virus. **Table 3** summarizes the findings from in vitro experiments.

While convalescent plasma is variable and neutralization assays are not standardized, the impact of the mutations in B.1.351, P.1, and B.1.247/B.1.429 are consistent across multiple studies and assays, indicating potential for immune evasion from pre-existing immunity, particularly for B.1.351. Additionally, P.1 emerged in Manaus, Brazil, an area that was estimated to have ~75% seroprevalence18 and P1 is estimated to have a reinfection rate of ~16-21%18,24.

Impact on vaccines: neutralizing antibodies

There is concern about how well vaccines will protect against the VOCs. Like Table 3, **Table 4** summarizes the in vitro findings on neutralization with serum from vaccinated individuals.

One note on the Sinovac CoronaVac: in an independent study, at 5 months post-vaccination, there was no neutralizing activity against P.145 . The other studies referenced in Table 4 used specimens collected 2 weeks after the last dose of vaccine so it is difficult to completely compare the findings although the serum from the CoronaVac study was still able to neutralize a non-P.1 virus45.

As with the convalescent plasma, the biggest impact on multiple vaccine types, was from B.1.351. P.1 and B.1.427/B.1.429 also showed decreased neutralization, while B.1.1.7 had the least impact. Likely the major mutations driving this phenotype are E484K, K471N, and L452R which are located in the receptor binding domain and are in neutralizing epitopes. Additional mutations in the RBD and NTD of B.1.351 likely contribute to the dramatic decrease in neutralizing titers.

Impact on vaccines: efficacy trials

While the neutralization studies serve as a good proxy for understanding the impact of VOCs on vaccine-induced immunity, data from efficacy trials and effectiveness during vaccine rollout are the best to inform the impact of VOCs on the vaccine's ability to protect from infection and disease. Efficacy trials were still ongoing for AstraZeneca ChAdOx1 nCoV-19, J&J Ad26.COV2.S, Novavax NVX-CoV2373, and Sinovac CoronaVac when the VOCs emerged.

B.1.1.7: There was minimal impact on the efficacy of AstraZeneca ChAdOx1 nCoV-19 (70.4% B.1.1.7 versus 81.5% non-B.1.1.7 efficacy against symptomatic disease)53. However, it was noted that efficacy against asymptomatic disease in the AstraZeneca ChAdOx1 nCoV-19 trial was significantly decreased with B.1.1.7 (28.9% B.1.1.7 versus 69.7% non-B.1.1.7)53. Despite this finding, viral load was decreased in asymptomatic cases of B.1.1.753. Novavax NVX-CoV2373 demonstrated similar efficacy for symptomatic COVID-19 (85% B.1.17 versus 89% non-B.1.1.7) and, importantly, was 100% effective against severe disease with B.1.1.759.

B.1.351: Trials of the AstraZeneca ChAdOx1 were halted in South Africa after it was demonstrated that the vaccine had only 10.4% efficacy against B.1.1351 for mild to moderate illness54. J&J Ad26.COV2.S had 64% efficacy against moderate to severe illness

	B.1.1.7 (20I/501Y.V1)	B.1.351 (20H/501Y.V2)	P.1 (20J/501Y.V3)	B.1.427/B.1.429 (CAL.20C)
Convalescent plasma	0-3.8[%,&] 27,34-38,39,40	**6-400**[%,&] 28,33,41-44,45	2.5-6.5[%,&] 37,38,40,45, ,40	4-6.7[&] 4

Table 3. Impact of VOCs on convalescent plasma neutralization. Data shown as a fold reduction of the neutralization titer to the wildtype D614G virus (WT). Key: no change = not significant, [%]pseudovirus, [&]live virus, [numbers] = reference, nd = no data (yet).

VOC→	B.1.1.7 (20I/501Y.V1)	B.1.351 (20H/501Y.V2)	P.1 (20J/501Y.V3)	B.1.427/B.1.429 (CAL.20C)
Vaccine↓				
Moderna mRNA-1273	1-2[%,&28,46]	9.7-12.4[%,28,47,46, 48, 49]	2.3-4.8[%,&,29,46]	1.8-2.8[%,&,46,47,50, 49]
Pfizer BNT162b	1-3.3[%,&28, 31,40,51,49]	5.9-10.3[%,&31,51,49,46,50,48]	1-3.8[%,&,31,29,49]	1.8-4[%,&,4,47, 49, 52]
AstraZeneca ChAdOx1 nCoV-19	2.3-8.9[&49,53]	4-11[%,&49,54]	2.9[%,&49]	nd
J&J Ad26.COV2.S	nd	nd	nd	nd
Sputnik V	2 (increase)[%55]	6.1[%55]	nd	nd
Novavax NVX-CoV2373	2.1[%,56]	14.5[%,47]	nd	2.5[%,47]
ZF2001	nd	1.4[&,57]	nd	nd
Sinopharm BBIBP-CorV	1.4[&,58]	0.4-1.5[&,57]	nd	nd
Sinovac CoronaVac	0.5[&,58]	0.3[&,58]	nd	nd

Table 4. Impact of VOCs on vaccinated sera neutralization. Data shown as a fold reduction of the neutralization titer compared to the wildtype D614G virus (WT). Key: no change = not significant, [%]pseudovirus, [&]live virus, [numbers] = reference, nd = no data (yet). **Vaccine types:** mRNA (Moderna mRNA-1273 and Pfizer BNT162b), adenovirus vector (AstraZeneca ChAdOx1 nCoV-19, J&J Ad26.COV2.S, and Sputnik V), protein subunit (Novavax NVX-CoV2373 and ZF2001), inactivated virus (Sinopharm BBIBP-CorV and Sinovac CoronaVac).

in South Africa (95% of infections in placebo and vaccine caused by B.1.351) compared to the 72% efficacy in the US (no B.1.351 at the time)60. Importantly, efficacy of severe/critical disease was only modestly impacted (85.9% in the US versus 81.7% in South Africa)60. Novavax NVX-CoV2373 was 50.4% effective against symptomatic COVID-19 and 60.1% effective in HIV-negative individuals, which was lower than what was found in the UK, however, it was still 100% effective against severe disease61.

P.1: The J&J Ad26.COV2.S trail was also conducted in Brazil and efficacy against moderate to severe illness was 68.1% (versus 72% in US) and 87.6% against severe/critical disease (versus 85.9% in the US) 60. Post hoc sequence analysis revealed the predominant strain was P.2 (69% of cases in vaccine and placebo arms) so no firm conclusions about efficacy against P.1 can be made. The P.2 variant does have the E484K mutation, however. Similarly, Sinovac CoronaVac had decreased efficacy in Brazil (51%) versus Turkey (91%) against symptomatic disease62. However, no information on viral genotype make up was available. Importantly, Sinovac CoronaVac had 100% efficacy against severe disease in Brazil62.

Impact of vaccines: effectiveness

In addition to the efficacy data, data is also emerging on vaccine effectiveness against the VOCs. For an excellent discussion on efficacy versus effectiveness, please refer to dr. Aly Diana's January newsletter article. Efficacy data refers to the controlled clinical trial data while effectiveness data refers to the data that occurs in the real world. Effectiveness data is being collected in areas where vaccine rollout has occurred.

Widespread vaccination with the Pfizer BNT162b has occurred in the UK and Israel where B.1.1.7 is the predominant strain (≥80% of viruses). In the UK, in healthcare workers, vaccination with 2 doses was associated with an 85% reduction in risk for symptomatic disease63. There has also been a reduction in hospitalizations and death64. This is important as B.1.1.7 has been associated with more severe disease (see Table 1).

In Israel where a massive vaccination campaign has occurred, a significant reduction in asymptomatic and symptomatic cases has occurred in addition to hospitalizations, severe COVID-19, and deaths65. An in-depth study on the impact of vaccinating adults >60 years of age showed that despite the B.1.1.7 variant being 45% more transmissible, mass vaccination of 80% of older adults with at least one dose of Pfizer BNT162b in 38 days resulted in a dramatic reduction in cases in that population66. Looking across the entire vaccinated population (≥ 16 years of age), Pfizer BNT162b was shown to be 91% against asymptomatic and 97% against symptomatic infection67. While the study did not specify viral genotyping, during this time, 80% of cases were attributed to B.1.1.7.

In refined analyses on the genotypes of breakthrough infections, it was demonstrated that breakthroughs after 2 doses of the vaccine were more likely to occur with B.1.351 than B.1.1.7 (8 cases versus 1 case), however, B.1.351 remains below 2% of viruses68.

Another population wide study in a setting with mass vaccination using the Pfizer BNT162b took place in Qatar where 50% of cases are B.1.351 and 44.5% are B.1.1.7. Vaccine effectiveness in those

fully vaccinated for any documented infection (asymptomatic or symptomatic) was 75% for B.1.351 (95% CI: 70.5-78.9) and 89.5% for B.1.1.7 variant was 89.5% (95% CI: 85.9-92.3). Further, vaccine effectiveness against severe disease from any SARS-coV-2 virus was 97.4% (95% CI: 92.2 to 99.5)

In California where 69% of viruses sequenced were B.1.1.7, B.1.427, or B.1.429, vaccine efficacy with either Moderna mRNA-1273 or Pfizer BNT162b was found to be 86% after 2 weeks after 2 doses69. In cases of breakthrough infection, 23 (7%) received BNT162b2 and 13 (4%) received mRNA-1273, however, only 8 (2%) were fully vaccinated with either product69.

In Manaus, Brazil where 75% of specimens are P.1, a study of healthcare workers receiving at least one dose of Coronavac was had adjusted vaccine effectiveness of 49.6% (CI: 11.3-71.4)70.

Concluding remarks

From the data presented in the cited studies, the B.1.351 variant is the largest concern for immune evasion followed by P.1 and B.1.427/B.1.429. There is much less to little concern for immune evasion of B.1.1.7 unless there is the E484K mutation. For certain, while virus neutralization, vaccine efficacy, and vaccine effectiveness are be impacted by VOCs and future VOCs, widespread vaccination will play a key role in curbing the spread the virus. As variants arise by chance, the less opportunity for chance, the better. Additionally, even with VOCs that have increased transmissibility, such as B.1.1.7, widespread vaccination has been demonstrated to be effective at decreasing cases and spread71. Finally, booster vaccines are in development against B.1.351 and show promising results in animal studies72 and cross-reactive neutralization has been demonstrated across VOCs, which demonstrates that a booster could be efficient in protecting against multiple variants with common mutations including the E484K73. As was discussed in January, in addition to vaccination, it's important to continue other public health measures including masking, good hand hygiene, and distancing.

Postscript: Surging cases in India and B.1.617

As this article was being written, a new VOC (WHO)/VOI (CDC) emerged and therefore is being highlighted on its own.

While India had relatively low numbers of SARS-CoV-2 cases, an incredible second wave occurred starting at the end of March 2021 with a peak of over 400,000 cases per day in early May. Early in the surge, multiple variants were identified in different areas: B.1.1.7 in Punjab and Delhi, B.1.618 in West Bengal, and B.1.617 in Maharashtra. B.1.617 quickly replaced B.1.618 in West Bengal74. Detailed sequence analysis revealed a rapid increase in a the common Spike signature mutations (G142D, L452R, E484Q, D614G and P681R) of the newly emerged lineage B.1.617 during February and March 2021, particularly in Maharashtra75.

B.1.617 has three sub-lineages: B.1.617.1, B.1.617.2, and B.1.617.3. All three contain Spike mutations L452R and P618R. L452R is located in the receptor binding domain and is found in the B.1.427/B.1.429 discussed previously. P618R is located in the furin cleavage site. B.1.617.2 and B.1.617.3 also contain a substitution at the 484 of E484Q76. **Table 5** breaks out the mutations.

Lineage or Sub-lineage	Spike mutations
B.1.617 20A	L452R, E484Q, D614G
B.1.617.1 20A/S:154K	(T95I), G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H
B.1.617.2 20A/S:478K	T19R, (G142D), Δ156, Δ157, R158G, L452R, T478K, D614G, P681R, D950N
B.1.167.3 20A	T19R, G142D, L452R, E484Q, D614G, P681R, D950N

Table 5. B.1.617 and sublineages. The nomenclature is Pangolin followed by Nextstrain. The predominat Spike mutations are shown. () indicate the mutation is not found in all sequences of viruses from that sublineage.

Molecular Dynamic simulations of the interaction of the Spike protein with the ACE2 receptor show the L452R and E484Q increase the stability of the interaction and therefore could impact viral entry77. However, in vitro experiments with pseudoviruses demonstrated decreased viral entry efficiency compared to the Wuhan reference. The P681R mutation in the furin cleavage site increases syncytia formation76.

In the hamster model, B.1.617 showed higher viral titer, increased lung pathology, and increased disease severity (body weight loss) compared to B.178. According to a report from Public Health England, B.1.617.2 has at least the same transmissibility as B.1.1.7, which is estimated to be about 50% more transmissible than previous variants79.

B.1.617 with L452R and E484Q is resistant to neutralization with bamlanivimab (LY-CoV555)80 and has decreased neutralization with casirivimab (REGN10933)81. Both monoclonals have FDA EUA as combination therapy (Bamlanivimab + Etesevimab (LY-CoV016) and Casirivimab + Imdevimab (REGN10987)) and the combinations retain activity with a slight decrease in activity with the Bamlanivimab + Etesevimab80.

Neutralization in live virus assays with sera from recipients of the inactivated Covaxin BBV152 against the B.1.617 was 1.98-fold lower than the D614G and 1.8-fold lower than B.1.1.782. Live virus neutralization assays show a 6.5-fold decrease in neutralization with convalescent plasma compared to the Washington reference strain. Two studies have shown decreased neutralization with sera from the mRNA vaccines (Moderna mRNA-1273

and Pfizer BNT162b) 83, including a 7-fold decrease in live virus neutralization compared to the Washington reference strain.81

In Delhi, where healthcare workers were vaccinated with the AstraZeneca ChdOx-1 vaccine, one case report showed breakthrough infection during the March-May wave in 30 healthcare workers. Of those, 12 were infected with B.1.617.2 within several days of each other. Sequence analysis revealed that those 12 were almost identical indicating a single transmission event83. Importantly, no severe disease was observed.

Given these findings, B.1.617 will need to be continued to be monitored as a VOC (WHO)/VOI (CDC).

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INA-RESPOND Newsletter

BOOST YOUR VACCINE WITH EXERCISE!

By: Edrick Purnomo Putra

During this worldwide COVID-19 pandemic, the COVID-19 vaccine has become one of the most talked-about topics. As we know, vaccination is a way to obtain immunological protection against a particular infectious disease by using certain biological preparation to provoke our body's active immune response. Vaccines have been used worldwide since many years ago to prevent many life-threatening infectious diseases as a part of national and international public health policy.1 Despite the controversy in public about the COVID-19 vaccine, getting vaccinated is one way to protect ourselves from this pandemic besides practicing health protocols. Vaccine is also needed to achieve herd immunity. Once herd immunity is reached, the whole community will be protected, including those vulnerable and who cannot get vaccinated. A large portion of the community needs to be vaccinated to achieve herd immunity, and this proportion varies with each disease. Currently, the proportion of the population that needs to be vaccinated to begin inducing herd immunity against COVID-19 is still unknown. However, it is encouraged that we get as many people as possible to be vaccinated.2

Since the currently available COVID-19 vaccines have different efficacy, and we do not have the privilege to choose either of them due to the limited availability, we must think of a way to boost the vaccine effect. The current studies related to the COVID-19 vaccine are still limited; therefore, we need to look at previous studies to compare and find answers. It is stated that environmental, behavioral, and nutritional factors will influence how individuals respond to a vaccine.3 Physical activity and exercise appear as promising factors to increase vaccine efficacy, yet many debates have also emerged on this matter. Some studies show that exercise may enhance promising immune responses after vaccination. On the contrary, other studies have found that exercise does not affect antibody response. Even worse, the public is afraid and questioning whether exercise may have a deleterious effect on vaccine efficacy.

To investigate the relationship between exercise and physical activity in vaccine response, let us talk about the extreme opposite poles first. How do athletes with regular training and a high level of physical activity respond to a vaccine? A recent study of elite athletes vaccinated with tetravalent influenza vaccine in 2020 demonstrated that the athletes show a more pronounced (4.1 fold) peak of vaccine reactive CD4 T-cell level in one week than controls (2.3 fold). A more pronounced significant increase in CTLA-4 expression in athletes also affected the specific cytokine profile. Athletes also showed a greater increase in neutralizing antibodies. This study indicated that elite athletes with high frequency and intensity of regular training had enhanced vaccine response.4 The writer has also written another study showing that influenza vaccines given to elite athletes are effective and safe, whether given 2 hours or 24-26 hours after training. This means that exercise after vaccination will not impair the immune response.5

Another extreme pole would be the elderly, who are vulnerable to infection and tend to be sedentary. A study using trivalent influenza vaccine in adults aged 62 and older categorizes the elderly into three groups: active (≥20 minutes vigorous exercise, ≥ 3 times weekly), moderately active (regular exercise with less intensity and duration), and sedentary. The result demonstrated that anti-influenza IgG and IgM are greater in active participants than moderately active or sedentary participants in two weeks post-immunization. Peripheral blood mononuclear cells (PBMC) were cultured in vitro with influenza vaccine to elicit antigen-specific response, and the proliferation was the lowest in the sedentary group.6 Another study comparing older men with intense training, moderate training, and no training lifestyle concluded that intense and moderate training older men showed significantly higher antibody titers to the three vaccine strains post-vaccination than no training older men. There were also higher titers against B and H1N1 strains in the trained groups before vaccination.

Additionally, there were higher proportions of seroprotected individuals in the pooled trained groups at 6 weeks and 6 months post-immunization. There were no significant differences between the moderate and intense training groups.7 Another study compared two groups of elderly between moderate cardiovascular exercise group (60-70% maximal oxygen uptake) and flexibility-balance training. Although no difference was observed at peak post-vaccination anti-influenza HI titers, cardiovascular exercise resulted in a significant increase in seroprotection 24 weeks after vaccination, whereas flexibility-balance training did not. The study also reported no differences in reported respiratory tract infections. On the other hand, the

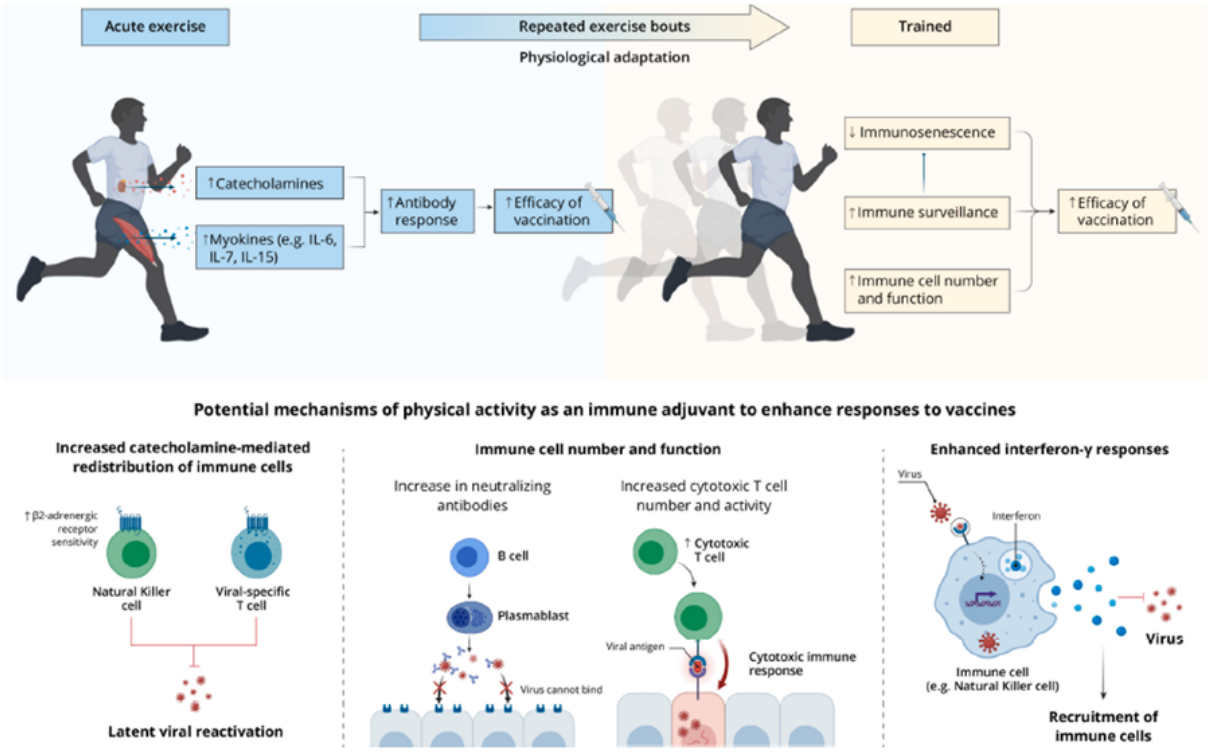

Figure 1. Possible immunological mechanism explaining the regular and acute bout of exercise performed before vaccination.16

exercise group exhibited reduced overall illness severity and sleep disturbance.8 From these studies, we can see that elderly with regular physical activity, at least in moderate intensity, show better immune parameters post-vaccination.

What about in general population? A study in mice showed that exercise enhances vaccine-induced antigen-specific CD4+ T cell cytokine production and proliferation in all lymphoid organs examined without changes in cell distribution in any organ.9 This result gives hope on coupling moderate exercise with vaccination to enhance vaccine efficacy in humans. However, studies in humans show various results. Younger adults appear to show less effect of regular exercise on the immune function when examining vaccine responses. However, it is worth noting that the robust response to most vaccinations in young, healthy adults may well mask any more subtle effects of exercise. In contrast, in older adults with weaker immune function, immunosenescence, and greater variability, the immune enhancement effects are more notable.10 Nevertheless, a systematic review and meta-analysis in 2021 revealed that regular physical activity, moderate to vigorous, is associated with reduced risk of community-acquired infectious diseases and infectious disease mortality in the general population, enhances the first line of defense of the immune system, and strengthens the potency of vaccination.11

While regular and long-term exercise exhibit promising benefits of immune-enhancing response, studies on acute bouts of exercise and its effect on vaccine response exhibit conflicting results. A study revealed that 45-minute brisk walking (>55% age-predicted heart rate) before vaccination does not affect antibody response to either influenza or pneumonia vaccine in 4 weeks post-vaccine administration for both younger and older adults.12 Another study with young adult samples comparing control (no exercise) with eccentric exercise done immediately, 6 hours and 48 hours prior to receiving trivalent influenza vaccine resulted in no differences in cell-mediated immunity among the groups.13 However, an analytic review concluded that acute exercise can be used as an adjuvant to the influenza vaccine and showed that immune responses are enhanced by a bout of acute exercise before inoculation, especially in vaccines that normally produce a weak immune response. It is hypothesized that eccentric exercise, performed using the muscles where the vaccine is injected, improves the subsequent immune response by inducing a pro-inflammatory environment in the muscles.14 It is worth noting that regardless of these conflicting results, none of the studies exhibit a deleterious effect of acute bouts of exercise on vaccine efficacy.15

Even though the effect of acute bouts of exercise on vaccine efficacy may not be clear enough, other studies display the benefits of reducing vaccine adverse reactions. A study with older adult samples showed that performing a 45-minute moderate-

intensity exercise prior to influenza vaccine decreases the vaccine adverse reactions after administration compared to control.17 Another study with younger adults receiving HPV and influenza vaccine exhibited reduced reported adverse reaction after administration for local and systemic adverse reactions. Reduced adverse reactions reported in the study were tenderness, pain, swelling, days of feeling ill, reduced appetite, and fever.18 CDC has also suggested using or exercising the arm to reduce pain and discomfort after the vaccine shot.19

After reviewing all the available studies described above, what message can we take? Exercise can become a low-cost and effective adjuvant for vaccines. Regular, moderate to vigorous physical activity is associated with reduced risk of infectious disease and mortality, enhances the first line of defense of the immune system, and increases vaccine efficacy, especially for those with weaker immune systems. Meanwhile, despite the contradicting results in the studies, acute bouts of exercise may enhance immune response, especially in vaccines that normally produce a weak immune response and decrease both local and systemic vaccination adverse reactions. It is also worth noting that vaccines given before or after exercise will likely have no negative effect on vaccine efficacy. Therefore, it is advisable that you stick to your usual workout routine and do not try to exert yourself more than you normally do. There is no reason to stop or reduce your exercise as long as no major adverse effects occur. In addition, for those who have not started exercising, there is no better moment than right now to start moving. Combining exercise, vaccination, and strict health protocols may be the answer to help lessen the impact of pandemics, such as the recent COVID-19.

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INA-RESPOND Newsletter

POLICY BRIEF, POLICY BRIDGE

By: Aly Diana

COMIC CORNER

As scientists, we have our own mumbo jumbo language to explain how important our researches are. Unfortunately, our encrypted way of communicating our results is generally too difficult to decipher by laypersons and, more importantly, by most policymakers.

To make an impact, first thing first, if we want people to listen, we need to speak the same language. It is a very obvious one, but sometimes we need a sweet reminder time after time.

However, making a good policy brief, the one that would be read and understood by intended audiences, is not only about the language – and it is something new that we need to learn further. Most of us have relatively little training in utilizing our clinical experience and scientific knowledge to impact policy, regardless of our interest in health policy. Developing a policy brief is one approach that health professionals may use to draw attention to important evidence that relates to policy. A policy brief is a short, to-the-point, jargon-free document written for non-specialists. It presents research or project findings to policy actors, highlighting the relevance of the specific research to policy and offering recommendations for change. Policy briefs act as a business card for researchers, presenting important research findings and a researcher's background in a concise and appealing way, the first step to establishing a good reputation and repeat consultations with policy actors.

There are three proposed steps to make a real impact using a policy brief: 1) planning and understanding our audience; 2) writing a policy brief; 3) getting our policy brief out there. When we create the planning, please consider the aim of our policy brief, which can range from changing policy to raising awareness of an issue. Most policy actors want relevant solutions to policy brief; therefore, a policy brief should clearly lay out evidence-informed solutions, which are realistic, feasible within the current political climate, and cost-effective. When writing a policy brief, please make sure that it is concise, clear, and easy to read; keep everything the reader needs to know is on the first page; highlight the benefits that our recommendations will have (to the policy system, to those affected by the policy, and more generally, e.g., economically and environmentally). Another thing, write a policy brief soon after research has been published to capitalize on the study's momentum and novelty.

Then, the way we distributed our policy brief may differentiate whether it will be read or end up in recycle bin. Send it in paper form and via email to a named person, and most importantly, follow up the policy brief. Personal contact with a policy actor can make a real difference. In addition, use social media and the internet to promote a policy brief, for example: by uploading the policy brief on our website, writing a blog about the research findings/ recommendations, and advertising the brief via other social media sites. Building an online presence, especially using social media, is a key way to develop your profile as a valued expert by increasing your access to policymakers.

This article is briefer than a policy brief, but there are a lot of resources to help us improve our ability. Again, this is only a sweet reminder for us to start exploring how and then writing our policy brief. For the more experienced ones (who are reading this), hopefully, you can give us some training or share your skills with us.

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The Indonesia Research Partnership on Infectious Disease newsletter is an internal bulletin of INA-RESPOND research network intended to disseminate information related to the network's studies, activities, and interests to all members of the network as well as its sponsors and related parties.

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