Acta Biomed 2022; Vol. 93, N. 1: e2022018 DOI: 10.23750/abm.v93i1.12224

SARS-CoV-2 Variants of Concern Increased Transmission and Decrease Vaccine Efficacy in the COVID-19 Pandemic in Palembang Indonesia

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Abstract. *Background and aim:* The number of COVID-19 cases surging despite the large scale of health promotion campaigns. This study aimed to find disease transmissibility and affected vaccine efficacy associated with the mutation of the SARS-CoV-2 variant of concern. *Methods:* The study was a descriptive temporal survey design with secondary ecological data: the whole-genome sequence (WGS) from the Global Initiative on Sharing Avian Influenza (GISAID) and COVID-19 data from the Palembang City Health Office website. Bioinformatics software was used to detect mutations. *Results:* Palembang submitted 43 whole genome sequences, 13 of which were Pangoline sequences classifications. *Conclusions*: The two concern variations, Alpha and Delta, were associated with increased transmissions and decreased vaccination efficacy using temporal analysis. Regulations governing the relaxation of mobility restrictions should be based on high rates of testing and tracing, and universal vaccination programs should require that all received two doses of any vaccines as fast as possible. (www.actabiomedica.it)

Key words: outbreak, contagious, immunity, temporal analysis, variant of interest

Background

The Coronavirus Disease 2019 (COVID-19) was first identified in December 2019 in Wuhan, China, when a vast amount of severe pneumonia cases were reported (1). The number of COVID-19 cases rapidly increased, and the virus spread beyond Wuhan to more than 200 other countries around the world, spurring the World Health Organization (WHO) to declare the virus a global pandemic on March 11, 2020 (2). By late August 2021, there had been over 214 million infections and 4.47 million deaths (3). Indonesia is still battling the COVID-19 pandemic (4). Authorities reported the first case of COVID-19 infection in March 2020 in Jakarta, and by the end of April, the virus had spread throughout the country (5). Apart from the human mobility factor, the high transmission rate can be caused by SARS-CoV-2 mutation (6).

The international community was shocked by the outbreak of the United Kingdom variant in December 2020 (7), and the virus went on to mutate from Alpha and Gamma variants before evolving into the Delta variant (8). Multiple spike protein mutations are correlated with increased transmissibility of the SARS-CoV-2 virus (9). The SARS-CoV-2 membrane (M), envelope (E), nucleocapsid (N), and spike (S) proteins (encoded by the ORF5, ORF4, ORF9 and ORF2 genes, respectively) are critical structural components

of the virus, as well as being required for viral genome packaging and infectivity (10). Genomic epidemiology has been suggested to be essential for identifying SARS-CoV-2 transmission (11).

Statistics indicate a rise in daily reports despite the South Sumatran government's health promotion effort (12). In this research, we looked at the development of mutations in the SARS-CoV-2 genome over twelve months. We demonstrate that the number of transmissions per variation grows with time. The emergence of variants of concern (VOCs) gradually increased in prevalence from early 2021, including further evolved versions of the British (B.1.1.7) and Indian (B.1.617.2) VOCs, and this emphasizes the importance of a dual mitigation and vaccination strategy, as well as the need for a rapid response. Appropriate interventions to increase positive community practices in preventing COVID-19 transmission in Indonesia, particularly in the South Sumatra Province, need to be enforced.

Methods

Bioinformatics analysis was combined with a descriptive temporal survey design for this ecological secondary data study. This research used the SARS-CoV-2 (S2) whole-genome sequence (WGS) obtained from the Global Initiative on Sharing Avian Influenza (GISAID) EpiCoV database (Germany) public services website (13), and COVID-19 case data was gathered from the Palembang City Health Office website (14). Until the beginning of August 2021, both data collection methodologies were completed by downloading databases. Samples from South Sumatra had to meet the S2 WGS inclusion criteria, while partial WGS and uncompleted WGS were excluded.

Bioinformatics software was used to detect mutations, with no human specimens or animal experiments. The Genious Prime software was used to translate the nucleotide sequence and analyze the aligned similarity (15). The nucleotide sequences were translated into protein sequences using the Genious translate tool, and the sequences corresponding to Spike Protein (SP) were assigned. Inkscape® was used to visualize the protein mutation in SARS-CoV-2 SP (1273 aa), with the hCoV-19/Wuhan/Hu-1/2019 (NC 045512.2) S gene represented as a reference. According to the guidance of the WHO, mutations were investigated for the variant of concern or interest (Table 1) (16).

Result and Discussion

SARS-CoV-2 Variants of Concern, Alpha and Delta

As of August 01, 2021, the total number of WGS generated data from the province of South Sumatra (Indonesia/SS) was 43. There were two variants of concerns (VOCs) and several variants of interests (VOIs) discovered. The Alpha (B.1.1.7) and Delta (B.1.617.2) VOCs were discovered in 1 and 20 specimens, and the VOI Kappa (B.1.617.1) in 1 specimen (Table 2).

A variant genome is a genome with a specific collection of mutations that have evolved through time. The Centers for Disease Control and Prevention (CDC) has classified SARS-CoV-2 variants into three categories: interest, concern, and high consequence (17). VOCs refer to the circumstances of increase in COVID-19 transmissibility or a change in the virus's

Table 1. Single Letter Codes of Amino Acid Changes at Specified Position and Variant of Alpha, Beta, Gamma, Delta and Kappa

Variant	Mutation						
	69-70 deleted	**K417 (N/T)**	**L452 (R)**	**E484 (K/Q)**	**N501 (Y)**	**D614 (G/R)**	**P681 (H/R)**
B.1.1.7 (or alpha)	69-70 deleted			K	Y	G	H
B.1.351 (or beta)		N		K	Y	G	
B.1.1.28.1 (or gamma or P.1)		N/T		K	Y	G	
B.1.617.2 (or delta)			R			R	H
B.1.617.1 (or kappa)			R	Q		G	H

Table 2. Tabulation and Date of Accession ID with a Mutation in Spike Protein, Detection of the Variant of Concern and Detection of Variant of Interest

No	Date of specimen	Accession ID	Protein Mutation	No	Date of specimen	Accession ID	Protein Mutation
1	09/10/2020	EPI_ISL_833039	B.1	23	14/01/2021	EPI_ISL_2047554	B.1.466.2
2	04/01/2021	EPI_ISL_1257823	B.1.1.398	24	15/01/2021	EPI_ISL_1969249	B.1.617.2
3	04/01/2021	EPI_ISL_1257824	B.1.524	25	15/01/2021	EPI_ISL_2854671	B.1.441
4	04/01/2021	EPI_ISL_1257825	B.1.466.2	26	28/01/2021	EPI_ISL_2854669	B.1.466
5	05/01/2021	EPI_ISL_1169047	B.1.1.7	27	06/04/2021	EPI_ISL_2047572	B.1.466.2
6	05/01/2021	EPI_ISL_1257826	B.1.466.2	28	09/04/2021	EPI_ISL_1915576	B.1.214.2
7	05/01/2021	EPI_ISL_2854667	B.1.459	29	09/04/2021	EPI_ISL_2047573	B.1.470
8	07/01/2021	EPI_ISL_2047507	B.1.466.2	30	04/06/2021	EPI_ISL_2931744	B.1.466.2
9	08/01/2021	EPI_ISL_1969244	B.1.617.2	31	10/06/2021	EPI_ISL_2931745	B.1.617.2
10	08/01/2021	EPI_ISL_2047508	B.1.466	32	10/06/2021	EPI_ISL_3070868	B.1.466.2
11	08/01/2021	EPI_ISL_2047509	B.1.470	33	11/06/2021	EPI_ISL_2931728	B.1.617.2
12	08/01/2021	EPI_ISL_2854672	B.1.36.19	34	11/06/2021	EPI_ISL_2931755	B.1.617.2
13	09/01/2021	EPI_ISL_2047510	B.1.466.2	35	11/06/2021	EPI_ISL_2931790	B.1.617.2
14	09/01/2021	EPI_ISL_2047511	B.1.466.2	36	12/06/2021	EPI_ISL_2931736	B.1.466.2
15	09/01/2021	EPI_ISL_2047512	B.1.459	37	12/06/2021	EPI_ISL_2931764	B.1.466.2
16	12/01/2021	EPI_ISL_1969245	B.1.617.2	38	12/06/2021	EPI_ISL_2931782	B.1.466.2
17	13/01/2021	EPI_ISL_2047551	B.1	39	13/06/2021	EPI_ISL_2931775	B.1.617.2
18	13/01/2021	EPI_ISL_2047552	B.1.466.2	40	17/06/2021	EPI_ISL_3070869	B.1.466.2
19	13/01/2021	EPI_ISL_2854668	B.1.466.2	41	18/06/2021	EPI_ISL_3070867	B.1.617.2
20	13/01/2021	EPI_ISL_2854670	B.1	42	29/06/2021	EPI_ISL_3070870	B.1.466.2
21	14/01/2021	EPI_ISL_1969250	B.1.617.1	43	30/06/2021	EPI_ISL_3070871	B.1.617.2
22	14/01/2021	EPI_ISL_2047553	B.1.466.2				

epidemiology; or infections with increased virulence or diseases with a different clinical presentation; or the effectiveness of public health and social initiatives such as vaccine efficacy. VOI or variant under investigation (VUI) is a variant that is being studied because of its association with known phenotypic implications (including epidemiology, antigenicity, or virulence or changes that have or potentially harm available diagnostics). The Delta variant genome was discovered in India in October 2020. Prior to the VOI designation on May 11, 2021, it received VOC classification on April 4, 2021 (18). The Delta variant was first documented in Palembang on January 08, 2021, in the stage when it was a VOI.

The VOC of Alpha and Delta and the VOI Kappa were circulating in the early stage of its emergence in Palembang city. The Alpha, Beta, Gamma, Delta, and other letters of the Greek alphabet were assigned to help identify the virus's ongoing mutation (19). A consensus exists on how to name the SARS-CoV-2 phylogenetic diversity. The first classification by GISAID, using the code as the mutation clade, such as S and L, then mutated into G, OH, OR, GV, GR, and GRY; unfortunately, the complexity gradually increased over time (20). Based on SARS-CoV-2 genetic clade distribution over time and countries, the Nextrain website cannot fully accommodate the dynamic virus nomenclature (21). The *Phylogenetic Assignment of Named Global Outbreak Lineage* (Pangoline) categorization aids the tracking and understanding of SARS-CoV-2 global spread by focusing on active and spreading virus lineages and providing a comprehensive combination of virus clade

epidemiological information (22). Thirteen Pangoline category genome variants were discovered in Palembang (table 2), which are the B.1, B.1.1.7, B.1.1.398, B.1.214.2, B.1.36.19, B.1.441, B.1.459, B.1.466, B.1.466.2, B.1.470, B.1.524, B.1.617.1, and B.1.617.2.

Major concerns pertain to the variant impact on viral transmissibility, disease severity, reinfection rates (i.e., evasion of natural immunity), and vaccine efficacy (i.e., evasion of vaccine-induced immunity). Positive community testing in UK for SARS-CoV-2 totaled 1,146,534 (51%), indicating that the Alpha variant is more contagious than the original virus. (23). As a result of the resistance mutations arising in the receptor-binding domain (RBD), SARS-CoV-2 was able to evade antibodies, affecting RBD immunogenicity and rendering antibodies ineffective (24). The Beta (B.1.351) variant has three notable mutations in the spike RBD, which are K417N, E484K, and N501Y3 (25), whereas the Alpha only has the N501Y mutation (26) and the Gamma (P.1/B.1.1.28.1) variant (35 mutations with 17 amino acid changes) was described in Brazil (27).

The Incidence of High-Rate Transmission and Variant of Concern

The cumulative number of COVID-19 transmissions in South Sumatra by July 2021 was tenfold that of the last year's cases (Figure 1). The Alpha and Delta VOC were discovered in early 2021. A total of 1,146,534 (51%) of the 2,245,263 SARS-CoV-2 positive community tests have been done, indicating that the Alpha variant is a more contagious strain than the parental virus (23). The Alpha variant has a reproduction number 43-90% higher than preexisting variants (95% confidential intervals, 38-130%) (7). The reproduction number (R0) of the Alpha variant is 60% more transmissible than the 2.5. parental virus. Furthermore, the Delta variant is roughly 60% more transmissible than the Alpha variant, with an R0 of 6 or 7 causing herd immunity to reach a higher number, around 85% (28).

The Alpha variant was first detected on January 5, 2021, with the single-letter codes of amino acid changes at the specified position of 614 mutation D to G (Figure 2b, number 5). This Alpha variant is the first to be reported from Indonesia's submission to GISAID (29). Before the Genomic Surveillance Network launched in early 2021, Indonesian institutions submitted about 140 sequences (130 WGS). The Ministry of Health (MoH) reported the first six sequences in March 2020. Following the establishment of the Genomic Surveillance Network, the MoH and universities submitted 5626 sequences, with 5589 full WGS sequences made public (29). Reporting WGS and accurate assessments is costly, and reagents are in short supply during the early crisis.

The type of Alpha variant detected lacked the mutation on E484K (Figure 3c, number 5). The Alpha variant containing the E484K mutation may be more successful at reinfection. The E484K means amino acid changed at the specified 484 position from E to K, and the E484K mutation is considered the escape mutation. The E484K mutation, among other things, can weaken the immune response and decrease the duration of the neutralizing antibody response. The E484K mutation has been found in several variants, including the Beta and Gamma (30). The major variants should be minimized by creating next-generation vaccines with different spike sequences and using different viral antigens in the formulation (31). The Alpha variant was still found in Indonesia until July 2021.

Palembang samples did not contain the Beta and Gamma variants; however, the Delta variation was discovered on January 8, 2021. The Delta strain has been observed in Indonesia with a frequency of 25% since January 7, 2021 (29). The Delta variant has a mutation P to R at position 681 (Figure 2c, number 9). Delta variants pose a double menace, presenting a higher risk of transmission and a lower vaccine efficacy level than the Beta variant (32). People who have had the Beta or Gamma variants are still at risk of getting re-infected with the Delta strain (33).

Controlling SARS-CoV-2 transmission has involved social isolation and limiting population movement. A quarantine policy was applied for individuals who have had close contact with SARS-CoV-2 patients in Palembang (34). Continual social distancing had significant benefits in countries where mobility was clearly linked to transmission (35). Many countries have implemented a lockdown to stop the SARS-CoV-2 virus from multiplying exponentially, lowering R0 to zero.

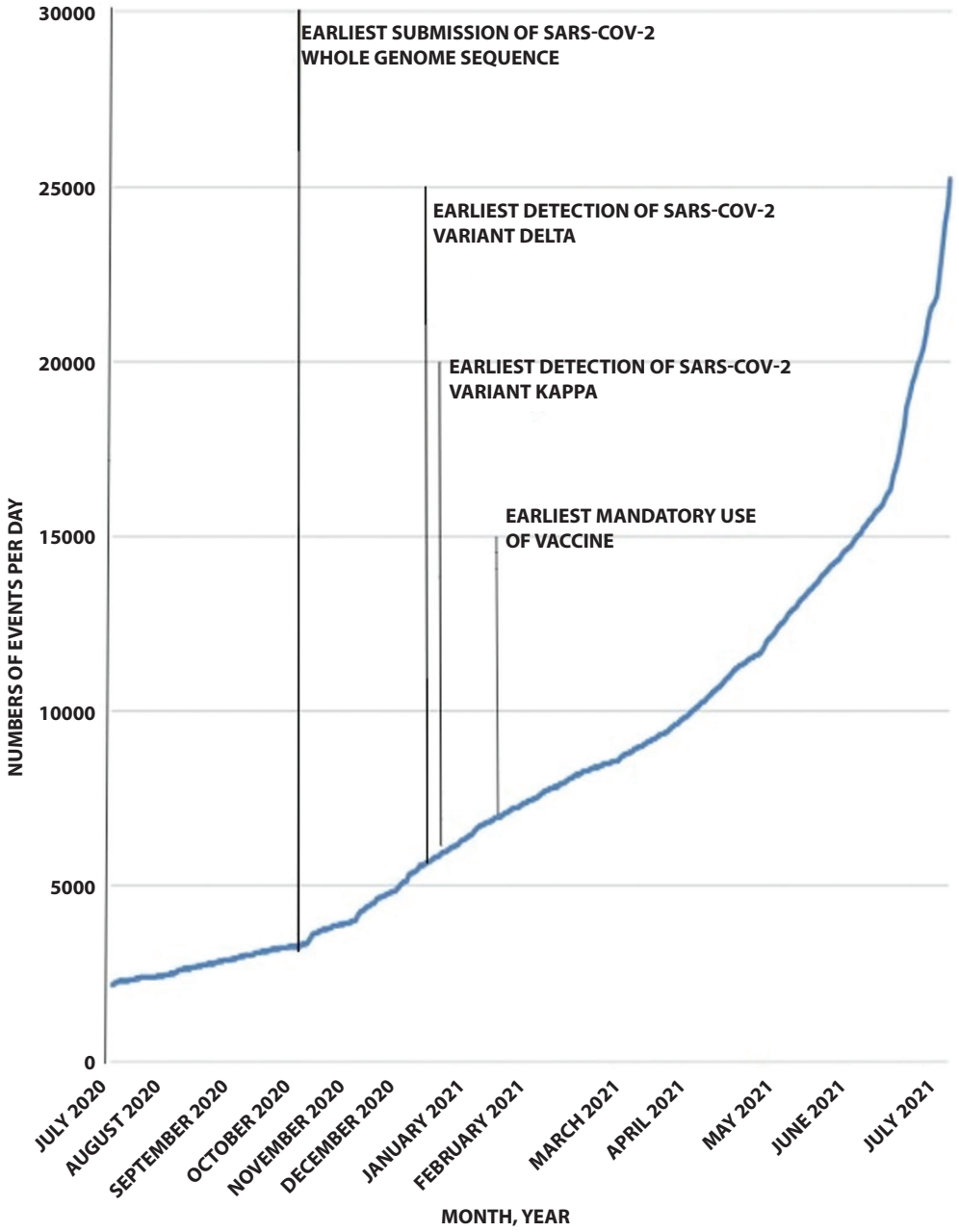

Figure 1. The Number of COVID-19 events per day, Earliest Detection 0f SARS-CoV-2 the Delta Variant of Concern was January 8, 2021, and The National Vaccine Campaign has been Commenced on January 14, 2021.

Physical separation and strict control over leisure activities (such as dining out) are required to exit lockdown successfully (36,37). Educational institutions and other large organizations are implementing effective contact tracing, shorter testing times, and targeted testing of high-risk classes, leading to fewer false negatives (38).

Social isolation, lockdowns, and mobility restriction interventions have significant societal and economic consequences. South Sumatra's government has relaxed regulations to provide people with more opportunities to improve their economic and social well-being (34). A larger share of resources should go to

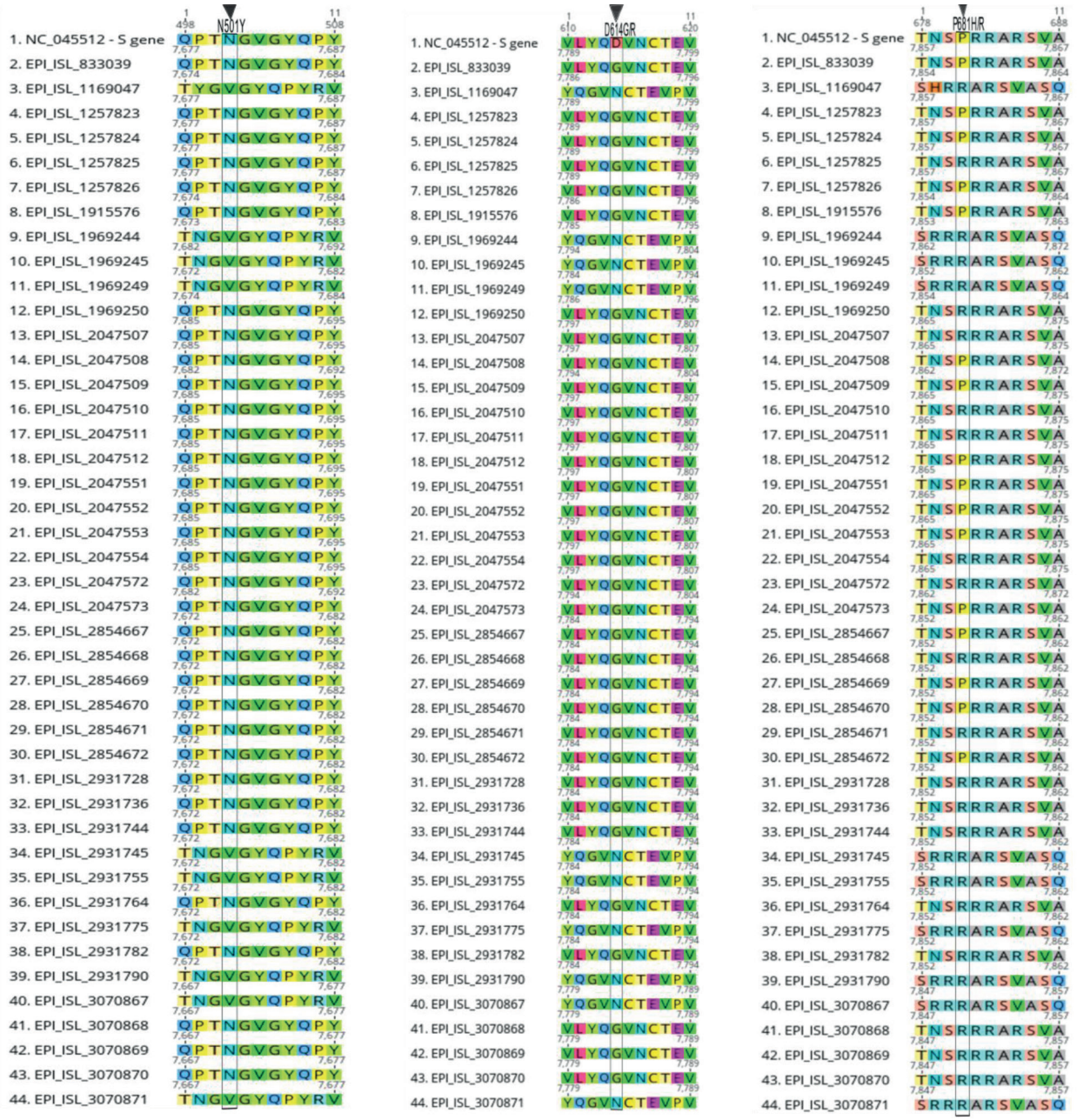

Figure 2. Single Letter Codes of Amino Acid Changes at Specified Position and Proposed Effect of Increase Transmission, shown in Black Column (a) 501 Mutation N to Y; (b) 614 Mutation D to G or R; (c) 681 Mutation P to H or R.

more impoverished areas (39). No evidence was found linking staying at home with a lower the number of deaths per million in any of the 87 different regions in 98% of the world studied. Regional differences in treatment methods and the virus's natural course may have contributed to pandemic fatality (40). After months of "lockdown" due to the COVID-19 pandemic, reopening society requires balancing social reopening with nonpharmacological measures to reduce interpersonal contact (41). The weekly alternations are timed to correspond with the natural SARS-CoV-2 disease timescales, allowing most infected people to be effectively isolated at the peak of infection (42). The success of relaxation of mobility restrictions and restoration

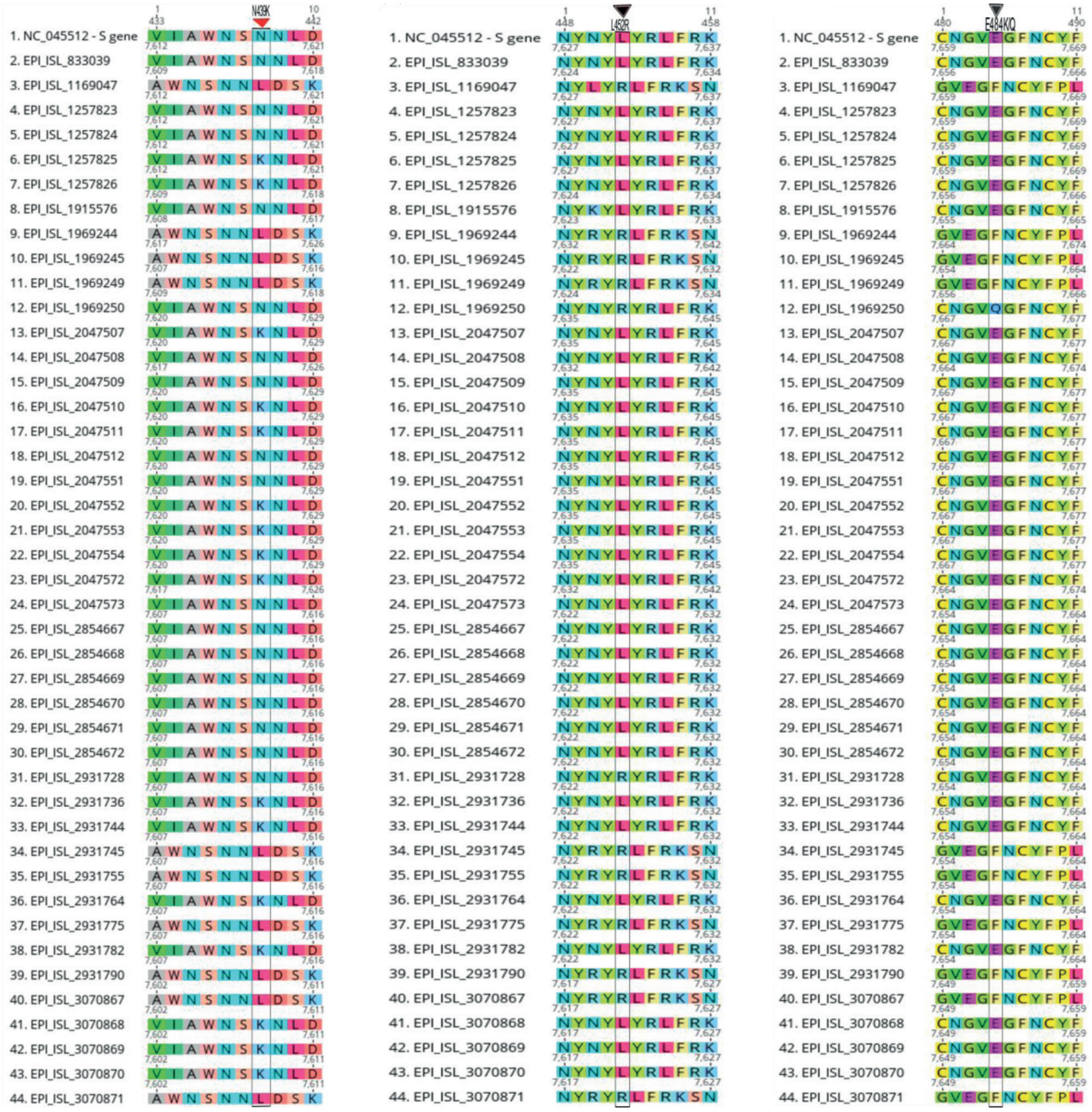

Figure 3. Single Letter Codes of Amino Acid Changes at Specified Position and Proposed Effect of Decreased Neutralization, shown in red column (a) 439 mutation N to K; (b) 452 mutation L to R; (c) 484 mutation E to K or Q.

of high mobility depends upon transmission control, high testing and tracing rates, high quarantine compliance, short testing and tracing delays, and moderate to high mask use (43). Relaxing mobility restrictions may increase the danger of transmission in localities with low testing and tracing rates.

The Campaign of SARS-CoV-2 Vaccination and Variant of Concern

The national vaccine campaign has been started on January 14, 2021. High vaccine efficacy is expected against the pathogen, the effects of infection, and the

dynamics of the transmission cycle. The vaccine's efficacy was shown in randomized control trials (RCTs) through a proportional reduction in disease between vaccinated and unvaccinated people (44). Five human Phase 3 SARS-CoV-2 vaccine studies have shown high efficacy. Among these Polack, BNT162b231 and Baden, and mRNA-1273 were 94.6%, 94.1%, and 91.6% effective, respectively. Using data from the United Kingdom, South Africa, and Brazil, the other two vaccines Voysey and ChAdOx21 discovered a 70% efficacy rate and a 66.7% efficiency rate (45). Vaccine efficacy against evolving variant strains may be lower, necessitating vaccine modification and faster vaccine rollout. The efficacy of mRNA-1273 against B.1.1.7 infection in Qatar was 88.1% after the first dose, while the efficacy against B.1.351 infection was only 61.3% (46).

The VOCs Alpha and Delta circulated in the city around the embarking of vaccination timelines (Figure 1). The type of Delta variant detected was with the E484K mutation (Figure 3a, number 16). The N439K mutation maintains SARS-CoV-2 virulence and fitness (47). A neutralizing monoclonal antibody approved for emergency use by the FDA is resistant to N439K mutation (48). The Delta variant is partially resistant to monoclonal and polyclonal antibodies arising from previous SARS-CoV-2 infection or vaccination (49). Because of the N439K mutation, antibodies and polyclonal sera from people who have recovered from infection are less effective.

The Beta and Gamma variations were not detectable in samples from Palembang; meanwhile, Indonesia has less than 0.5% of the Beta strain as of January 25, 2021. However, despite protection from the Alpha variant, individuals who have been immunized are still at risk from Beta infection (50). Immune suppression appears to play a role in the vaccines' ability to partially neutralize the SARS-CoV-2 virus (50). The Beta is a lineage with changes in two immunodominant domains of the spike protein, enabling it to completely avoid three therapeutically important antibodies and resist neutralization but not the binding to convalescent plasma (51). The Gamma strain was relatively resistant to neutralization when tested against multiple therapeutic monoclonal antibodies, convalescent plasma, and vaccine sera. A cryo-electron microscopy-determined crystal structure revealed that the Gamma trimer only adopts a conformation in which one of the receptor-binding domains is in the up position (52). Comprehensive evaluation and the availability of reagents may improve the tracing and tracking of VOCs.

In Palembang, the vaccine used was CoronaVac® (Sinovac), which had an efficacy of 63.5% (53) and the second dose coverage was 17.02% (54). A total of 25 RCTs corroborate the overall efficacy and safety of all COVID-19 vaccines and offered solid data-driven evidence to support the ongoing global public health effort to vaccinate the whole population against the virus (55). The vaccine efficacy gap widened in the first dose, but following two immunization doses, only small differences in vaccine efficacy were seen for the dominating variants of the Delta and Alpha. Efforts have been made to increase vaccination uptake by giving two doses of the vaccine among vulnerable populations (56). Due to the perceived risk of COVID-19, it may be necessary to increase subsidization for vaccine coverage, (57), especially because the cost of the COVID-19 vaccine may contribute to its low uptake (58).

This study has limitations. First, it was very challenging to collect and store the routine clinical SARS-CoV-2 PCR samples. Many patients' early samples were unavailable. Thus the description regarding the rise of VOC or VOI level can not be determined. Secondly, better monitoring and representative evaluation are expensive, and reagents are sparse during a pandemic. As a result, the exact dominating circulating strain could not be verified.

Conclusions

Palembang submitted 43 whole genome sequences, 13 of which were Pangoline sequence classifications. Two VOC, Alpha and Delta, were associated with increased transmission and decreased vaccination efficacy using a temporal analysis. Regulations governing the relaxation of mobility restrictions should be based on high rates of testing and tracing, and universal vaccination programs should require that all people received two doses of any vaccines as fast as possible.

Acknowledgments: We would like to thank the Health Department of Palembang municipality and South Sumatra province and the all-Indonesian institutions that submitted whole-genome sequences of SARS-CoV-2 data to GISAID so that we could use them for analysis and to GISAID for making the SARS-CoV-2 data available. The study was supported by Unggulan Profesi Research Grant Universitas Sriwijaya (SP DIPA-023.17.2.677515/2021), with the Rector's Decree Number of 0014/UN9/SK.LP2M. PT/2021, and Grant RisetMu Research and Development Education of PP Muhammadiyah batch 5/2021 with contract number: 0842.194/PD/I.3/C/2021

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Received: 2 September 2021
Accepted: 30 September 2021
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