

The other side of Covid 19 vaccines: Can Omicron variant be a live attenuated vaccine?

* Tuan Anh Nguyen¹, Ram K. Gupta²

¹Institute for Tropical Technology, Vietnam Academy of Science and Technology, Hanoi, Vietnam.

²Kansas Polymer Research Center, Department of Chemistry, Pittsburg State University, Pittsburg, Kansas, United States

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*Corresponding author: Tuan Anh Nguyen, Institute for Tropical Technology, Vietnam Academy of Science and Technology, Hanoi, Vietnam. Email: ntanh@itt.vast.vn

1. Introduction to Omicron Variant

New viral strains can be created due to mutation or swapping of genetic components (alteration in the nucleotide sequence of their genome) when two or more viruses infect the same cell in nature. These phenomena are known as antigenic drift and antigenic shift, respectively [1-3]. The mutations of SARS CoV2 have been identified through genome analysis collected from COVID 19 patients. Since December 2020, there are 5 main variants of concern (VOC), such as Beta (first outbreak: South Africa, earliest cases: May 2020); Alpha (first outbreak: UK, earliest cases: September 2020); Delta (first outbreak: India, earliest cases: October 2020); Gamma (first outbreak: Brazil, earliest cases: November 2020) and Omicron (first outbreak: South Africa, earliest cases: November 2021) [4]. These variants contribute to the continuation of the COVID 19 pandemic.

Covid vaccines started to be distributed worldwide in January 2021 to curb the pandemic. Along with vaccines, separate neutralizing antibodies (Abs) were also developed to treat COVID 19 patients. For genome analysis of SARS CoV2 and its variants, the researchers focused on the S gene since it encodes the spike protein that interacts with the ACE 2 receptor of the host and promotes the entry of the virus inside the host cell.

Most of the current vaccines and neutralizing Abs are targeted towards the S protein and some treatment to block the replication of the virus inside the host cell [5]. The S protein comprises 16 subdomains, out of which the receptor binding domain (RBD) is most important as it interacts with the angiotensin converting enzyme 2 (ACE2) of the host [5]. The Beta variant has 10 mutations in the S gene. The Alpha variant has 13 mutations in the S gene. The Gamma variant has a total of 11 mutations in the S gene [5]. In the case of the Delta variant, it has 8 or 9 mutations in the S gene [6].

The newly found Omicron has an unusually large number of mutations, several of which are novel and a significant number of which affect the spike protein targeted by most current COVID 19 vaccines [7-9]. The Omicron variant has a total of 60 mutations compared to the original Wuhan variant [4]. 32 mutations affect the spike protein. Many of those mutations had not been observed in other previous strains [10, 11]. This level of variation has led to concerns regarding its transmissibility, immune system evasion, and vaccine resistance. As of 15 December 2021, the variant has spread to over 80 countries. Most initial reports indicate that the variant causes less serious disease than previous strains [4]. Please note that among the 4 above mentioned variants, only Omicron is identified after the

massive vaccinations worldwide. In most countries, the vaccination campaign started in late December 2020/ January 2021, but the massive shots have been carried out in April/May 2021, due to the availability of vaccine distribution [12].

Previous work reported that the number of infections increased daily after starting each mass vaccination, then the more injections the COVID 19 positive cases increased [12]. It was difficult to explain when new SARS CoV 2 variants have not appeared since the Delta variant last year (before Omicron). The decline in the protective effect of each vaccine over time (about 4 to 6 months after full dose) is unlikely to be a valid reason. It just only reflects the ineffectiveness of the current vaccines. The most logical reason is “ineffective vaccination” or which might have weakened the immune system against the SARS CoV 2. This hypothesis has been confirmed experimentally 6 months ago by researchers from Britain’s Francis Crick Institute (London, UK) [13]. It was found that the Pfizer COVID 19 vaccine destroyed T cells, and weakened the immune system. This finding would explain why side effects are worse after the second dose of the COVID 19 vaccine. For the cases of reinfection with COVID 19, their recovery could be slower than the patients without vaccination [14 16]. On the other hand, this finding also helps to understand the reason why the new cases increase after vaccination in many countries/regions. Inappropriate vaccine/vaccination would damage the (invisible) shield immunity (shield of immune people around those who are susceptible).

In addition, new evidence has revealed that the Omicron variant was already present in Western Europe well before the first cases were detected by South African scientists and flagged it to the world [17 24]. Please also note that the vaccination rate in UK and Netherlands are very high, as 70% and 74%, respectively [25]. These vaccination rates are higher than the value of the estimated ‘herd immunity threshold’ (~ 60–70% of the population gaining immunity, either through vaccinations or past exposure to the virus [26]). Whereas, in South Africa, the

vaccination rate is only 26% [25]. This fact and data from genome analysis suggest that Omicron might relate to the massive vaccination in Europe by the current ineffective vaccines.

2. Omicron Originated from EU After Massive Vaccinations?

2.1. Effect of massive vaccinations on covid cases worldwide

In April 2021, more than 1.2 million coronavirus genome sequences from 172 countries and territories have now been shared on GISAID, a popular online data platform (GISAID: Global Initiative on Sharing Avian Influenza Data). Since these countries are submitting data from many parts of the world, we can “watch how the virus spreads through the world, and see if control measures and the vaccines still work” [27].

As reported in the previous work [12], the more injections the COVID 19 positive cases increased. Various countries have been analyzed, such as India, Israel, Germany, UAE, South Africa, Canada, Saudi Arabia. In most cases, the number of infections increased daily after 1 or two months from the vaccinated date of each mass vaccination. Thus the inappropriate vaccine/vaccination would damage the shield immunity (shield of immune people around those who are susceptible).

For comparison between the high and low vaccinated countries, we focus on the EU and the Southern African countries. As shown in Table 1, the number of infections (per 1 million population) increased with increasing vaccination rate in both EU and Southern African countries.

2.2. Omicron in EU

In the UK, the Omicron cases have been reported before the first detected case in South Africa. A triple vaccinated Israeli doctor believed that he caught the strain at a conference in London attended by 1,250 people on November 23 [21 24]. More than

10,000 cases of Omicron have been reported, with at least 10 people hospitalized. One person has died after contracting the variant, as the first death with Omicron in the world [29]. On December 16, 2021, another grim record for the COVID epidemic with 88,376 new cases has been reported, as 31.4% rise on the week. The number of Omicron cases rose to 11,708. Cases are doubling every one and a half days in London where 73.5% of Covid cases are now expected to be Omicron [30].

In the Netherland, Dutch health authorities found the new Omicron variant of the coronavirus in cases dating back as long as 11 days, indicating that it was already spreading in western Europe before the first cases were identified in Southern Africa [17 20]. Belgium and Germany have also said that sample tests confirm the variant was in those countries before South African health officials alerted the world on November 24, 2021, of its existence [17]. On December 15, 2021, the number of cases of the Omicron variant of COVID 19 in Denmark increased by

1,512 to reach a running total of 6,047 [31]. In Ireland, the share of Omicron variant cases of COVID 19 has almost doubled in two days to 27% [32].

Table 2 presents the Omicron variant cases in Europe and Southern African countries As shown in Table 2, the Omicron cases seem not to relate to the vaccination rate in both EU and Southern African countries. However, over half of Omicron cases in England occurred after two doses of vaccine [33]. Germany also confirmed cases of Omicron variant in vaccinated patients [34]. In Denmark, about 9% of patients infected with Omicron had received three doses of a Covid 19 vaccine, 75% two doses, while only 14% were unvaccinated [35]. In Table 2, as the logical reasoning fact, the highest number of Omicron cases have been reported in the 3 world leaders (UK, Denmark, and South Africa [36, 37]). in sequencing the coronavirus genome.

Countries	Total cases	Total cases/ 1 M pop	Total deaths	Vaccination rate (fully vaccinated)
UK	11,010,286	160,959	146,791	69.7%
Germany	6,669,370	79,234	107,772	69.6%
Netherlands	2,936,761	170,841	20,310	73.5%
Denmark	589,274	101,218	3,051	77.1%
Belgium	1,980,120	169,779	27,729	75.7%
Ireland	644,143	128,361	5,835	76.4%
Italy	5,282,076	87,549	135,178	74.5%
South Africa	3,231,031	53,498	90,226	26%
Botswana	197,644	81,653	2,424	42.6% (as of 15 Dec) 22.5% (as of 9 Dec)
Namibia	134,154	51,445	3,579	12.8%
Zimbabwe	182,057	11,995	4,759	20.1%

Table 1: Coronavirus cases and vaccination rate As of December 16, 2021 [25, 28]

Countries	Total cases (GISAID)	Total cases (other sources)	Vaccination rate (fully vaccinated)
UK	4,120	10,017	69.7%
Germany	102	77	69.6%
Netherlands	64	105	73.5%
Denmark	273	6,047	77.1%
Belgium	124	17	75.7%
Ireland	32	39	76.4%
Italy	17	13	74.5%
South Africa	1000	499	26%
Botswana	84	0	42.6% (as of 15 Dec)
Namibia	17	18	22.5% (as of 9 Dec)
Zimbabwe		50	12.8%

Table 2: Omicron variant cases in Europe and Southern African countries (As of December 16, 2021) [4]

2.3. Omicron in South Africa

Southern Africa is not a hotbed of variants it's just very good at sequencing and spotting them [38]. SARS CoV 2 was first detected in South Africa on March 5, 2020, in a traveler returning from Italy. The Omicron was identified first on November 11, among foreign diplomats who had traveled to Botswana. Then, it was found again by a team of scientists in South Africa on November 14, and they alerted world health leaders. The reality is that southern Africa is a top international powerhouse of COVID 19 surveillance in large part because the continent stood up innovative systems for tracking viral diseases and genetic mutations well before the coronavirus hit, tracing, and surveilling diseases including HIV, Ebola, and tuberculosis. The discovery of Omicron has highlighted the genomic surveillance capabilities of South Africa where scientists first discovered the beta variant in 2020 and were involved in the detection of the omicron variant.

South Africa's genomic sequencing capabilities heavily rely on the Network for Genomic Surveillance in South Africa, known as NGS SA, which is a network of laboratories, scientists, and academic institutions that have joined forces to ensure the public health responses to COVID 19 in South Africa have access to

the best possible scientific data. The initiative was launched in June 2020 when five of the South African National Health Laboratory Services' largest laboratories and their associated academic institutions in Bloemfontein, Cape Town, Durban, Johannesburg, and Tygerberg were awarded a grant by the South African government. The network has since expanded to include private diagnostic laboratories and other academic institutions within South Africa and beyond [39]. In South Africa, Omicron currently is responsible for about 70% of new COVID 19 cases, according to the studies in South Africa [40].

3. Omicron as a promising live attenuated vaccine?

One of the most indefatigable laws of nature is the law of natural selection. Regarding the evolution of viruses, viruses have short generation times, and many in particular RNA viruses have relatively high mutation rates (on the order of one point mutation or more per genome per round of replication). This elevated mutation rate, when combined with natural selection, allows viruses to quickly adapt to changes in their host environment. In genetics, the mutation rate is the frequency of new mutations in a single gene or organism over time [41, 42]. Studies have shown that treating RNA viruses such as poliovirus with ribavirin produces results consistent with the idea that the

viruses mutated too frequently to maintain the integrity of the information in their genomes [43].

The high mutation rate of HIV (Human Immunodeficiency Virus) is 3×10^{-5} per base and generation, coupled with its short replication cycle leads to a high antigen variability, allowing it to evade the immune system [44]. The estimate of the mutation rate of HIV 1 demonstrated that any single mutation conferring drug resistance should occur within a single day. Sanjuan et al. [45] reported the mutation rates of 23 viruses as substitutions per nucleotide per cell infection (s/n/c) and corrected for selection bias where necessary, using a new statistical method. The resulting rates range from 10^{-8} to 10^{-6} s/n/c for DNA viruses and from 10^{-6} to 10^{-4} s/n/c for RNA viruses [45].

Since the time that SARS CoV2 was first identified in December 2019, there are 5 main variants of concern, such as Beta, Alpha, Delta, Gamma, and Omicron. Before Omicron, both the Alpha and the Delta variants were observed to be more transmissible than previously identified viral strains [46]. Regarding the detected dates of VOC variants, before the vaccination campaigns, the mutation rate of VOC would be around 5 or 6 months (for Beta, Alpha, Gamma, and Delta). It is believed that Omicron has been generated after 5-6 months from the largest massive vaccination campaigns in the EU, where the vaccination rate was highest than other regions in the world. In early 2021, the new VOC could not be detected. Two possible reasons are i) low vaccination rate worldwide, and (ii) the dominant stage of Delta over other variants or the domestic variants in countries and regions.

By comparison between Omicron and Delta, the Omicron variant is much more transmissible than Delta [47, 48]. Major South African study concludes that the Omicron variant is more resistant to the vaccine but causes less severe illness [49, 50]. On December 13, 2021, the UK Prime Minister confirmed that only one person is known to have died in the world (after contracting the Omicron) [51]. This death case is too smaller as compared to

other variants and much lower than the death cases due to the vaccination [52-58]. Currently, the Omicron variant can likely outcompete the Delta variant [59], but it needs six more months to take over the Delta. As the case of competition between Delta and Alpha, since the first detected in October 2020, after 8-9 months, the Delta variant was the dominant strain worldwide [60]. In the case of Japan, the Alpha variant had replaced other variants in January 2021, then was dominated by Delta in September 2021 [61], after the first detection on April 20 [62]. Thus, now it is just a matter of time for the Omicron variant to replace others including the Delta.

Besides, the mathematical models indicated that pandemic influenza could spread globally only within 6 months. EU warned that Omicron to become dominant in Europe by mid January [63], or by March 2022 [64]. According to the World Health Organization (WHO) [64], a 1.5 times higher transmission compared to Delta could result in the Omicron variant being dominant in Europe within the next few months. On December 7, 2021, the Russian President cited experts who compare the Omicron to a live vaccine [65]. In addition to the current antiviral agents, 'virus against virus' strategy has been proposed as potential solution against Covid 19 [66, 67].

Thus, Omicron could be the effective live attenuated vaccine against SARS CoV2 (and its variants, like Delta and Alpha) in the next 6 months, then the COVID finally could be controlled.

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