

HOW SARS-COV-2 DELTA VARIANT WAS CURBED IN JAPAN. WILL OMICRON REPLACE IT?

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The SARS-CoV-2 Delta (B.1.617) variant emerged in the Indian state of Maharashtra at the end of¹ 2020 [1]. Currently, the sublineages of this variant include 146 sublines. On May 11, 2021, the WHO declared the SARS-CoV-2 B.1.167.2 variant to be a variant of concern (VOC) [2]. In accordance with the Nextstrain classification,[3] the Delta variant has three phylogenetic clades, such as 21.A, 21.I, and 21.J. 21J is currently prevailing in the world; its distinctive feature is mutation A394V in the non-structural nsp14 protein. This mutation in the 21J clade is likely to have enabled the Delta variant of SARS-Cov-2 to gain dominance around the world (see Fig. 1).

The fifth wave of the coronavirus pandemic in Japan has receded sharply and there are currently few cases (see Fig. 2) with sporadic deaths, while other countries are facing spikes. The 'Japanese phenomenon' has aroused vivid interest among researchers. Similar

phenomena of a drastic decline in COVID-19 incidence were also seen in other countries, such as Israel, New Zealand, India, Indonesia, etc. In some of the countries, this was due to mass vaccination campaigns, although the SARS-CoV-2 Delta variant caused a surge after the rapid decrease in incidence in countries with high percentage of vaccinated population. The Delta variant was determined to have gained the ability to evade vaccine-induced immunity because of mutations L452R and T478K in the S protein [5].

A group of researchers believe that the use of ivermectin can bring down COVID-19 cases and excess mortality rates [6]². On November 18, 2021, The Japan Times published an article by journalist Osamu Tsukimori about a hypothesis proposed by Professor Ituro Inoue of Japan's National Institute of Genetics. He argues that the Delta variant of SARS-CoV-2 has accu-

mulated too many mutations in the non-structural nsp14 protein in Japan and, therefore, it may have triggered 'self-extinction' [7]. It should be noted that Japan's prevailing subline of the Delta variant was AY.29 (see Fig. 2 a, b) with mutation V932A in the nsp3 protein, which is unique to the region [8]. The AY.29 sublineages became dominant in June 2021 [8]. The nsp3 protein of SARS-CoV-2 is known to suppress congenital immunity of its host, thereby contributing to the virus survival [9]. Mutation V932A in the Japanese subline of the Delta variant and mass vaccinations have been presumably a factor in sharply decreasing the incidence rate (see Table 2 c, d). It should be noted that the AY.29 strain is not widespread anywhere except for Japan.

Several publications in peer-reviewed journals focus on disappearance of the Delta variant in Japan. According to Sayeed, U.B. et al.[12] and Imamura, T. et al. [13], this is due to:

1. A nationwide state of emergency without a lockdown, but with school closures from April 14, 2021 until May 25, 2021, which was declared by Prime Minister Shinzo Abe;

2. Introduction of a retrospective cluster approach to detecting sources of primary infection focus and contacts to enable early implementation of anti-epidemic measures (in contrast to South Korea's

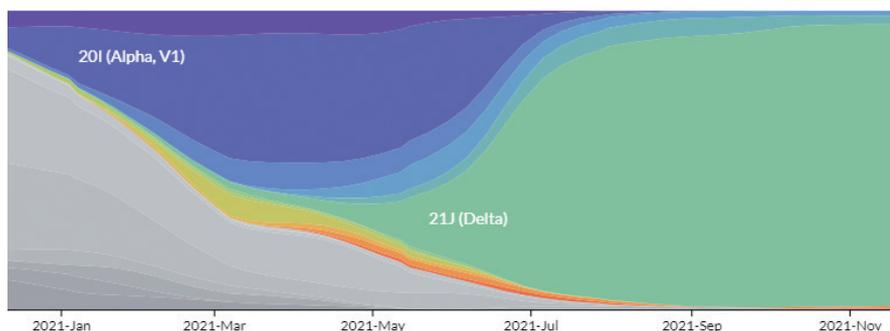


Figure 1. Global Evolution of SARS-CoV-2 Clades in %. Frequency of the 21J clade was 94% as of November 27,2021 [4].

¹ According to updated October data

² Note that this paper is a preprint

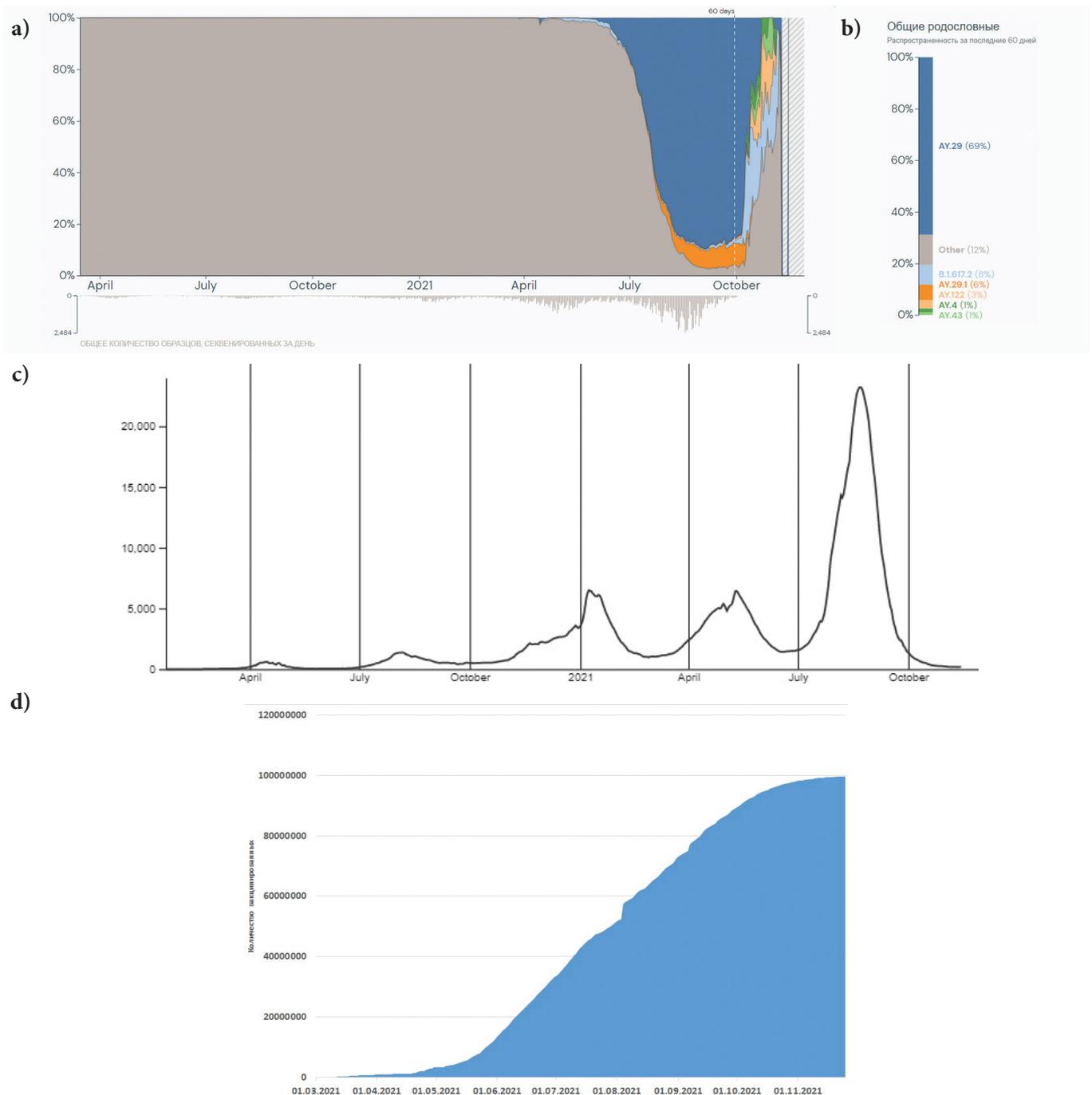


Figure 2. Frequency Dynamics (a), Percentage of SARS-CoV-2 Sublineages (b) and Daily COVID-19 Cases in Japan (c) [10], Number of Vaccinated People in Japan (d) (the chart is based on the available data [11]). Over 50% of the population received a vaccine at the peak of the fifth wave, with 99.65 million people (79.1%) got vaccinated by November 25, 2021 [11]

pooled testing strategy for identifying infection foci) and creation of a Cluster Response Team along with 536 consultation centers throughout the country;

3. The Three Cs Public Awareness Program. The Japanese Gov-

ernment encouraged remote work and also recommended the population to avoid traveling and refrain from visiting places designated with three Cs, i.e., closed spaces, crowded places, and close-contact settings. Later, it was recommended to

refrain from singing and loud conversations (3Cs+);

4. The high-quality and widely accessible health-care system. In order to reduce contacts with sick persons, they coordinated nationwide hotel involvement for isolating

contact persons and mildly ill individuals, with hospital robots widely used for patient care.

5. The Japanese Ministry of Health, Labor and Welfare released the COCOA mobile app to track COVID-19 contacts and infected people. It identifies a contact with a COVID-19 positive patient within 1 meter of proximity for at least 15 minutes, contains instructions and provides recommendations on what to do in different situations.

6. Japanese healthy lifestyle and traditions.

7. High mass vaccination coverage.

A dramatic drop in COVID-19 cases during the fifth wave in Japan is undoubtedly owing to a set of factors whose combination has resulted in such a sharp decline in COVID-19 incidence. It cannot be excluded that the AY.29 subline of the Delta variant has accumulated too many mutations in the error-correcting non-structural nsp14 protein and this has rendered it less virulent. It is also possible that ivermectin has played a certain role in reducing the incidence rate. In this regard, it should be noted that starting from the 7th edition of the Concept of COVID-19 Drug Therapy published by the Japanese Association for Infectious Diseases on February 1, 2021, ivermectin is named in the “Other Antiviral Preparations against COVID-19” section as an antiviral drug that can be used for treatment of COVID-19 [14]. The dosage of ivermectin administered in the prehospital phase in Japan and its impact on the epidemic process of coronavirus infection remain unknown. There is no doubt, however, that the break of the fifth wave in the country was due to a set of factors whose com-

bined effect has exceeded all expectations. Will Japan face the next wave? The country implements an effective quarantine control system at airports. A lot of coronavirus strains came to the country during the Olympic Games and none of them got widespread among the population [12].

The new B.1.1.529 variant (Omicron) of SARS-CoV-2 that was identified in early November raises concerns around the world. The WHO declared it a variant of concern (VOC) on November 26, 2021[15]. As of November 30, 2021, the GISAID database contains 182 genomes of the Omicron variant

from 14 countries, while the earliest positive sample was taken in South Africa on November 9, 2021 [16]. We have analyzed mutations of 177 genomes obtained from the GISAID database using the Coronapp web application [17]. The results of the study show that one sample has an average of 62 mutations, with a total of 224 various mutations found in all the samples³.

Mutations of the SARS-CoV-2 Omicron variant are published at <https://covariants.org/>. According to the data, the new coronavirus variant has 35 non-synonymous mutations within the spike protein, while it has only 3 mutations that are in common

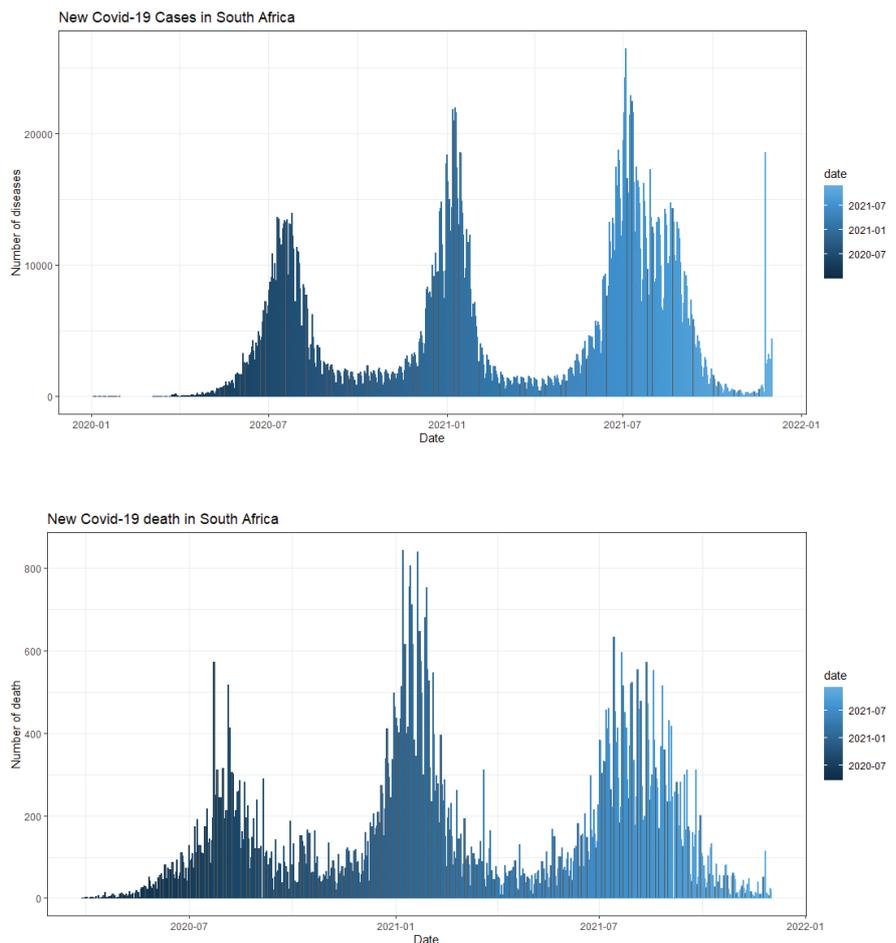


Figure 3. Daily COVID-19 Cases and Deaths in South Africa as of December 1, 2021 (WHO data [20]).

³ The data is sourced from GISAID participants and are available at <https://www.gisaid.org/>

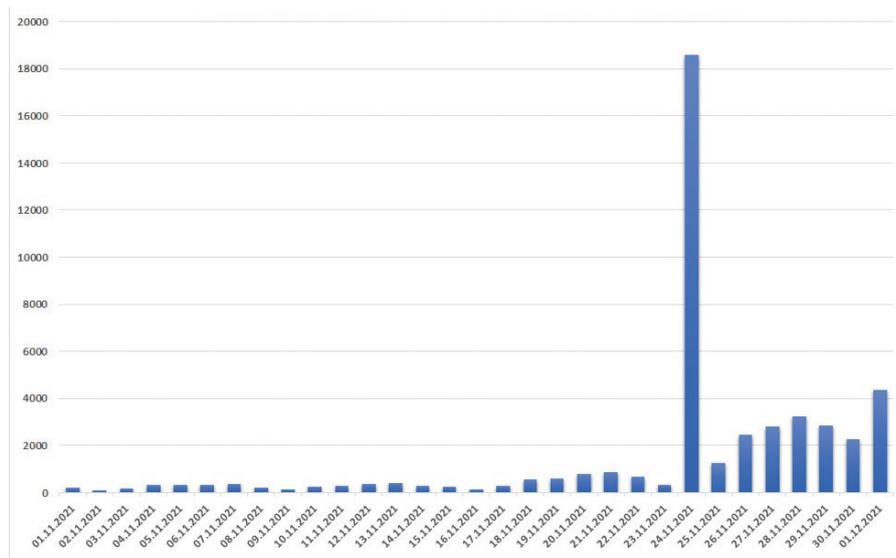


Figure 4. South Africa's daily incidence of Covid-19 over the past month

with the Delta variant [18]. Such a large number of mutations should undoubtedly change disease patterns and target organs. On November 28, 2021, the WHO published a Statement to note that it was not clear to date whether the new variant of SARS-CoV-2 was more transmissible than other variants, including Delta, and that the severity of its clinical manifestations was also unclear. According to preliminary data, the Omicron variant can increase COVID-19 reinfections [19]. In its Statement made on November 26, 2021, the Technical Advisory Group on SARS-CoV-2 Virus Evolution suggested that the new Omicron variant had an evolutionary advantage as compared to other variants; however, no new data has been published so far.

The monitoring of COVID-19 cases and deaths in the population of South Africa shows a moderate upward trend in incidence, while there is no clear picture of mortality growth (see Fig. 3 and Fig. 4). Like the Delta variant, Omicron has a mutation (I42V) in the non-structural nsp14 protein, which, according to our data, can be found in 93.2% out of 177 analyzed cases. Nsp14 contains encoded 3'-5' exonuclease, which corrects errors during replication and removes incorrectly bound nucleotides. Viruses lacking exoribonuclease activity are proved to be susceptible to lethal mutagenesis [21], and those coronaviruses that lack the ability to correct errors during replication are nonviable or, alternatively, lose their adaptabil-

ity or virulence [22]. In this regard, accumulation of the virus mutation in the non-structural nsp14 protein could disrupt its equilibrium.

Therefore, it should be noted that curbing the SARS-CoV-2 Delta variant in Japan has probably initiated extinction of the Delta variant and the pandemic. Whether Omicron will replace Delta has been unknown so far. In case of Spanish flu, mass mortality reached an end two years later, although up to 2% of the population died in some villages at the Spanish flu outbreak in Yakutia in 1925 [23]. If Omicron replaces Delta, COVID-19 may probably turn into a seasonal infection, provided that the majority of the world population gets vaccinated or get sick.

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