

Current global situation of SARS-CoV-2 variants circulation and future actions required in Japan

Katsutoshi Nakano*, Kenzo Takahashi

Graduate School of Public Health, Teikyo University, Tokyo, Japan

Corresponding author (*)

Katsutoshi Nakano

Graduate School of Public Health, Teikyo University, Tokyo, Japan

E-mail: sph-knakano@med.teikyo-u.ac.jp

Received May 31, 2021

Accepted June 24, 2021

Keywords: SARS-CoV-2 variants

Abstract

One year after the COVID-19 pandemic, the spread of SARS-CoV-2 variants is one of the challenging public health issues. Significantly, the Variant of Interest (VOI), which was reported since the end of 2020, has already been reported to increase transmissibility and disease severity in various articles and reports. As a result, the concern has been raised of decreasing the vaccine's efficacy, and it is necessary to monitor the latest research.

As the infection of SARS-CoV-2 variants is spreading in Japan, it is necessary to implement effective public health preventive measures, promote vaccination, expand sequencing to identify variants, and continue to be vigilant against new variants as a global issue.

Introduction

It has been almost one year since the WHO declared a pandemic of COVID-19 on March 11, 2020. As of May 27, 2021, the number of infected people is 160 million, and the number of deaths is three million¹⁾ worldwide, and the new coronavirus infection is still a significant public health issue globally, although vaccines have been developed.

The first case of B.1.1.7, one of the SARS-CoV-2 variants, was reported in the United Kingdom (U.K.) on September 20, 2020²⁾.

SARS-CoV-2 variants have become an important issue in Japan. For example, a case of B.1.1.7 was confirmed in a returnee from the U.K. to Japan on December 25, 2020, and as of April 5, 2021, more than 2,000 cases of SARS-CoV-2 variants have been reported in Japan³⁾.

In this article, we provide an overview of the SARS-CoV-2 variants, the characteristics of each variant, vaccine efficacy and discuss the actions required in the future.

Variants of SARS-CoV-2

SARS-CoV-2 is classified as an RNA virus that mutates at a

much higher rate than DNA viruses and other cellular organisms such as bacteria, with one to two nucleotide changes (mutations) occurring per month⁴⁾.

Although few mutations of public health concern were reported in the early stages of the pandemic, some of the currently identified SARS-CoV-2 variants have been reported to increase transmissibility and disease severity.

The CDC classifies important SARS-CoV-2 variants as Variant of Interest (VOI), Variant of Concern (VOC) and Variant of High Consequence (VOHC).

VOIs have been shown to have genetic changes that may affect infectivity, diagnosis and treatment, and vaccine effectiveness, while VOC is defined as those reported to increase transmissibility and disease severity. VOHC is defined as a VOC with clear evidence of reducing the effectiveness of conventional preventive measures and medical care, but no mutations belonging to VOHC have been reported to date⁵⁾.

Individual characteristics of each SARS-CoV-2 variants (Table 1)

The increased transmissibility and disease severity of SARS-CoV-2 variants are mainly due to the mutations increasing the binding affinity of the receptor-binding domain to the angiotensin-converting enzyme 2 (ACE2) receptor⁶⁾.

• B.1.1.7 variant (501Y.V1)

B.1.1.7, classified as one of the VOCs, was first identified in the U.K. on September 20, 2020. Subsequently, B.1.1.7 infection spread mainly in southeastern England, leading to a UK-wide lockdown on December 29, 2020⁷⁾. According to the results calculated from mathematical models, the B.1.1.7 mutation is estimated to be 43-90% (95%CI: 38-130%) higher effective reproduction number than existing strains⁸⁾, and various studies have reported a significant increase in mortality compared to existing strains⁹⁾.

On the other hand, a multivariate analysis of VOC cases in the E.U. did not show a significant increase in mortality but did report a higher risk of hospitalization in the age groups of 20-39 years and ICU admission in the age groups of 40-59 years¹⁰⁾.

• B.1.351 variant (501Y.V2)

This variant, B.1.351, which is included in the VOC as well as B.1.1.7, appeared around October 2020 during the second wave of the SARS-CoV-2 epidemic in South Africa and became dominant in mid-November, replacing the conventional strain¹¹⁾.

Table 1. Representative SARS-CoV-2 variants in Japan

Pango lineage	B.1.1.7	B.1.351	P.1 (B.1.1.28.1)	B.1.617
Nextstrain	20I / 501Y.V1	20H / 501.V2	20J / 501Y.V3	20A
Variant classifications (WHO) ¹⁶⁾	VOC	VOC	VOC	VOC
First Detected	England	South Africa	Japan (traveler from Brazil)	India
Transmissibility, disease severity	<ul style="list-style-type: none"> 43-90% higher effective reproduction numbers⁸⁾ High mortality or increase risk of hospitalization and ICU admission¹⁰⁾ 	<ul style="list-style-type: none"> Transmission rate is 1.5 times¹³⁾ Increased risk of hospitalization and ICU admission in some generations¹⁰⁾ 	<ul style="list-style-type: none"> Increased risk of hospitalization and ICU admission in some generations¹⁰⁾ 	<ul style="list-style-type: none"> There are concerns about increased infectivity due to the form of the mutation¹⁵⁾
Effectiveness of vaccines	Reduce the risk of symptomatic infections in the elderly ¹⁸⁾	Reduce the incidence of serious cases ²⁰⁾	Not enough data	Not enough data

As for B.1.1.7, B.1.351 and P.1 (B.1.1.28.1) Vaccines' sera can neutralize the N501Y mutant¹⁸⁾

Information on the transmissibility and severity of B.1.351 is limited at this time as of May 27, 2021. However, the risk of hospitalization in the age groups of 40-79 years and ICU admission in 40-59 years is high¹⁰.

The preprint paper reported that this mutant strain might have contributed to the increased mortality in the second wave in South Africa¹² and estimated a 1.50-fold higher transmission rate than conventional strains¹³.

• P.1 variant (B.1.1.28.1, 501Y.V3)

The P.1 variant was found in an airport screening of travelers arriving at Tokyo from Brazil on January 2, 2021¹⁴. The risk of hospitalization in the age group of 20-79 years and ICU admission in the age group of 40 years or older is high, and the risk of hospitalization in the age group of 20-39 years is exceptionally high with an adjusted OR 13.1 (95% CI 6.5-26.5) compared to existing strains¹⁰.

• B.1.617 variant

B.1.617, which was first identified in India in October 2020. Although no large scale observational or cohort studies have been done, B.1.617 is feared to have increased infectivity due to the form of the mutation in the receptor binding domain¹⁵. For this reason, It is classified as a VOI by the CDC but is classified as a VOC by WHO¹⁶ and Japan¹⁷.

Effectiveness of vaccines against SARS-CoV-2 variants

As mentioned above, VOIs and VOCs are of concern because they involve mutations in the receptor-binding domain (RBD) of the S-protein on the virus surface.

Since the S-protein is a major target of vaccines, there is concern that mutations at this site may reduce the effectiveness of vaccines.

However, several articles, including preprints, have indicated that the vaccine is effective. Among these, there is a report that sera from Pfizer/Biontech vaccinees can neutralize the N501Y mutant (mutations in B.1.1.7, B.1.351, and P.1)¹⁸, that vaccination with Pfizer/Biontech or Oxford/AstraZeneca vaccines significantly reduce the risk of symptomatic infection of SARS-CoV-2 in the elderly against the B.1.1.7 mutant strain¹⁹, and that vaccination with the Johnson & Johnson/Janssen Pharma vaccine may reduce the incidence of severe cases of B.1.351²⁰.

These studies suggest that the vaccines against SARS-CoV-2 available so far can have some effect on SARS-CoV-2 variants. However, given the existence of variants yet to be thoroughly investigated and the emergence of further variants, the information is not sufficient at this time to provide a definitive answer.

Infection status of the SARS-CoV-2 variant in Japan

The number of SARS-CoV-2 infected in Japan has been on the rise again since mid-March 2021. Initially, new infections were reported mainly in the Kansai region, and the number of new infections in Osaka reached a record high on April 14. The proportion of B.1.1.7 mutant strains in screening tests during this period was about 80% in Osaka and Hyogo, and about 30% in Tokyo²¹. The percentage of mutant strains reached 60% in Tokyo on May 12, 2021²², and by May 19, 2021, it was about 80% nationwide, suggesting that most infections have been replaced by mutant strains²³.

As shown above, most of the infections in Japan have been replaced by B.1.1.7, but the variant of concern is B.1.617. Infection with B.1.617 has been confirmed in persons with no history of overseas travel, and it is presumed that they were infected by community-acquired infection, and there is concern that the number of such cases will increase in the future¹⁷.

The world's preferred response to mutant strains

It is a concern that SARS-CoV-2 will continue to mutate and VOIs and VOCs will continue to emerge, and various experts have proposed countermeasures to deal with these situations.

The first requirement is to reduce the number of infections on an international basis. The more people who are infected, the more

opportunities the virus may have to mutate⁷. In order to fulfill this requirement, public health precautions must be taken that are as effective as previously. These include wearing masks, social distancing, hand washing, limiting access to high-risk facilities, and extensive testing and quarantine to rapidly identify and isolate infected individuals to SARS-CoV-2²⁴⁻²⁸.

Next, it is necessary to roll out vaccination to all parts of the world, including areas where vaccines are challenging to deliver and reduce the chance of infection^{24, 26-28}. In addition, the effectiveness of currently used and future vaccines against SARS-CoV-2 variants needs to be continuously monitored²⁸. For this reason, it is essential to track the variants that have been identified so far strictly and to widely promote enhanced surveillance to identify new variants through multilateral cooperation rapidly²⁴⁻²⁷.

Currently, the spread of some SARS-CoV-2 variants is a problem in Japan. It may even trigger the creation of a new variants in Japan. If the mutated strains spread to other countries, it will become a global health issue problem. Therefore, it is necessary to address SARS-CoV-2 infection not as a domestic problem.

Thus, we must continue to implement adequate public health precautions to control the spread of the diseases, promote vaccination, expand sequencing to identify mutant strains, and remain vigilant against new mutant strains.

Authors' contributions

K.N. and K.T. drafted the idea of this article.

K.N. drafted the first manuscript.

K.T. advised and revised the manuscript.

All the authors agreed to submit this article.

Conflict of Interest

Kenzo Takahashi reports personal fees from Novartis pharma, Japan, as a lecture reward, outside the submitted work. K.N. declares no conflicts of interest.

References (Marked* are preprinted papers)

- 1) World Health Organization, Coronavirus (COVID-19) Dashboard, <https://covid19.who.int/> (accessed May 27, 2021)
- 2) Public Health England. Investigation of novel SARS-CoV-2 variant 202012/01: technical briefing 3. <https://www.gov.uk/government/publications/investigation-of-novel-sars-cov-2-variant-variant-of-concern-20201201> (accessed May 27, 2021)
- 3) National Institute of Infectious Diseases, Japan. Epidemiological Analysis of New Mutant Cases Reported in Japan (1st Report). <https://www.niid.go.jp/niid/ja/diseases/ka/corona-virus/2019-ncov/2484-idsc/10279-covid19-40.html> (accessed May 27, 2021)
- 4) Genomic epidemiology of novel coronavirus-Global subsampling. <https://nextstrain.org/ncov/global?l%20=%20clock> (accessed May 27, 2021)
- 5) CDC. SARS-CoV-2 Variant Classifications and Definitions. 2021/5/17. <https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html> (accessed May 27, 2021)
- 6) Salim S. Abdool Karim, M.B., Ch. B, Ph. D. New SARS-Cov-2 Variants-Clinical, Public Health, and Vaccine Implications. *N Engl J Med* 2021; 384: 1866-1868
- 7) Diana Duong. What's important to know about the new COVID-19 variants? *CMAJ* 2021; 193 (4): E141-E142
- 8) Nicholas G Davies, Sam Abbott, Rosanna C Barnard, Christopher I Jarvis, Adam J Kucharski, James D Munday, Carl A B Pearson, Timothy W Russell, Damien C Tully, Alex D Washburne, Tom Wenseleers, Amy Gimma, William Waite, Kerry L M Wong, Kevin van Zandvoort, Justin D Silverman, CMMID COVID-19 Working Group; COVID-19 Genomics U.K. (COG-UK) Consortium; Karla Diaz-Ordaz, Ruth Keogh, Rosalind M Eggo, Sebastian Funk, Mark Jit, Katherine E Atkins, W John Edmunds. Estimated transmissibility, and impact of SARS-CoV-2 lineage B.1.1.7 in England. *Science*. 2021; 372 (6538): eabg3055.

- 9) Peter Horby, Iain Bell, Judith Breuer, Muge Cevik, Rob Challen, Nicholas Davies, Gavin Dabrera, John Edmunds, Neil Ferguson, Sebastian Funk, Andrew Hayward, Julia Hippisley-Cox, Ben Humberstone, Catherine Huntley, Jim McMenamin, Paul McKeigue, Graham Medley, Calum Semple. NERVTAG paper Update note on B.1.1.7 severity, February 11 2021. <https://www.gov.uk/government/publications/nervtag-update-note-on-b117-severity-11-february-2021> (accessed May 27, 2021)
- 10) Tjede Funk, Anastasia Pharris, Gianfranco Spiteri, Nick Bundle, Angeliki Melidou, Michael Carr, Gabriel Gonzalez, Alejandro Garcia-Leon, Fiona Crispie, Lois O'Connor, Niamh Murphy, Joël Mossong, Anne Vergison, Anke K Wienecke-Baldacchino, Tamir Abdelrahman, Flavia Riccardo, Paola Stefanelli, Angela Di Martino, Antonino Bella, Alessandra Lo Presti, Pedro Casaca, Joana Moreno, Vítor Borges, Joana Isidro, Rita Ferreira, João Paulo Gomes, Liidia Dotsenko, Heleene Suija, Jevgenia Epstein, Olga Sadikova, Hanna Sepp, Niina Ikonen, Carita Savolainen-Kopra, Soile Blomqvist, Teemu Möttönen, Otto Helve, Joana Gomes-Dias, Cornelia Adlhoeh, COVID study groups. Characteristics of SARS-CoV-2 variants of concern B.1.1.7, B.1.351 or P.1: data from seven EU/EEA countries, weeks 38/2020 to 10/2021. *Euro Surveill.* 2021 Apr 22; 26 (16): 2100348.
- 11) Hourriyah Tegally, Eduan Wilkinson, Marta Giovanetti, Arash Iranzadeh, Vagner Fonseca, Jennifer Giandhari, Deelan Doolabh, Sureshnee Pillay, Emmanuel James San, Nokukhanya Msomi, Koleka Mlisana, Anne von Gottberg, Sibongile Walaza, Mushal Allam, Arshad Ismail, Thabo Mohale, Allison J Glass, Susan Engelbrecht, Gert Van Zyl, Wolfgang Preiser, Francesco Petruccione, Alex Sigal, Diana Hardie, Gert Marais, Nei-Yuan Hsiao, Stephen Korsman, Mary-Ann Davies, Lynn Tyers, Innocent Mudau, Denis York, Caroline Maslo, Dominique Goedhals, Shareef Abrahams, Oluwakemi Laguda-Akingba, Arghavan Alisoltani-Dehkordi, Adam Godzik, Constantinos Kurt Wibmer, Bryan Trevor Sewell, José Lourenço, Luiz Carlos Junior Alcantara, Sergei L Kosakovsky Pond, Steven Weaver, Darren Martin, Richard J Lessells, Jinal N Bhiman, Carolyn Williamson, Tulio de Oliveira. Detection of a SARS-CoV-2 variant of concern in South Africa. *Nature.* 2021; 592 (7854): 438-443.
- 12) *Waasila Jassat, Caroline Mudara, Lovelyn Ozougwu, Stefano Tempia, Lucille Blumberg, MaryAnn Davies, Yogan Pillay, Terrence Carter, Rams Morewane, Milani Wolmarans, Anne von Gottberg, Jinal N. Bhiman, Sibongile Walaza, DATCOV Author Group, Cheryl Cohen. Increased mortality among individuals hospitalised with COVID-19 during the second wave in South Africa. *medRxiv preprint.*
- 13) *Carl A.B. Pearson, Timothy W Russell, Nicholas Davies, Adam J Kucharski, CMMID COVID-19 working group, W John Edmunds & Rosalind M Eggo. Estimates of severity and transmissibility of novel SARS-CoV-2 variant 501Y.V2 in South Africa. Retrieved from: (<https://cmmid.github.io/topics/covid19/sa-novel-variant.html>)
- 14) National Institute of Infectious Diseases, Japan. Brief report: new variant strain of SARS-CoV-2 identified in travelers from Brazil. Tokyo, Japan: National Institute of Infectious Diseases, Japan; 2021. <https://www.niid.go.jp/niid/en/2019-ncov-e/10108-covid19-33-en.html> (accessed May 27, 2021)
- 15) *Sarah Cherian, Varsha Potdar, Santosh Jadhav, Pragya Yadav, Nivedita Gupta, Mousmi Das, Soumitra Das, Anurag Agarwal, Sujeet Singh, Priya Abraham, Samiran Panda, Shekhar Mande, Renu Swarup, Balram Bhargava, Rajesh Bhushan, NIC team, INSACOG Consortium. Convergent evolution of SARS-CoV-2 spike mutations, L452R, E484Q and P681R, in the second wave of COVID-19 in Maharashtra, India. *bioRxiv preprint.*
- 16) World Health Organization, Weekly epidemiological update on COVID-19 - 25 May 2021, <https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---25-may-2021> (accessed June 12, 2021)
- 17) National Institute of Infectious Diseases, Japan. Report on B.1.617, a SARS-CoV-2 variant (2nd Report), <https://www.niid.go.jp/niid/ja/diseases/ka/corona-virus/2019-ncov/2551-lab-2/10353-covid19-44.html> (accessed June 12, 2021)
- 18) *Raveen Rathnasinghe, Sonia Jangra, Anastasija Cupic, Carles Martínez-Romero, Lubbertus C F Mulder, Thomas Kehrer, Soner Yildiz, Angela Choi, Ignacio Mena, Jana De Vrieze, Sadaf Aslam, Daniel Stadlbauer, David A Meekins, Chester D McDowell, Velmurugan Balaraman, Juergen A Richt, Bruno G De Geest, Lisa Miorin, Florian Krammer, Viviana Simon, Adolfo García-Sastre, Michael Schotsaert. The N501Y mutation in SARS-CoV-2 spike leads to morbidity in obese and aged mice and is neutralized by convalescent and post-vaccination human sera. *medRxiv.* 2021
- 19) Jamie Lopez Bernal, Nick Andrews, Charlotte Gower, Chris Robertson, Julia Stowe, Elise Tessier, Ruth Simmons, Simon Cottrell, Richard Roberts, Mark O'Doherty, Kevin Brown, Claire Cameron, Diane Stockton, Jim McMenamin, Mary Ramsay. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. *BMJ* 2021; 373: n1088
- 20) Jerald Sadoff, M.D., Glenda Gray, An Vandebosch, Vicky Cárdenas, Georgi Shukarev, Beatriz Grinsztejn, Paul A Goepfert, Carla Truysers, Hein Fennema, Bart Spiessens, Kim Offergeld, Gert Scheper, Kimberly L Taylor, Merlin L Robb, John Treanor, Dan H Barouch, Jeffrey Stoddard, Martin F Ryser, Mary A Marovich, Kathleen M Neuzil, Lawrence Corey, Nancy Cauwenberghs, Tamzin Tanner, Karin Hardt, Javier Ruiz-Guiñazú, Mathieu Le Gars, Hanneke Schuitemaker, Johan Van Hoof, Frank Struyf, Macaya Douoguih, ENSEMBLE Study Group. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. *N Engl J Med.* 2021 April 21.
- 21) National Institute of Infectious Diseases, Japan. Recent infection status of novel coronavirus infection (as of April 20, 2021), <https://www.niid.go.jp/niid/ja/diseases/ka/corona-virus/2019-ncov/10316-covid19-ab31th.html> (accessed June 12, 2021)
- 22) National Institute of Infectious Diseases, Japan. Recent infection status of novel coronavirus infection (as of May 12, 2021), <https://www.niid.go.jp/niid/ja/diseases/ka/corona-virus/2019-ncov/10356-covid19-ab34th.html> (accessed June 12, 2021)
- 23) National Institute of Infectious Diseases, Japan. Recent infection status of novel coronavirus infection (as of May 19, 2021), <https://www.niid.go.jp/niid/ja/diseases/ka/corona-virus/2019-ncov/10380-covid19-ab35th.html> (accessed June 12, 2021)
- 24) Viola Priesemann, Rudi Balling, Melanie M Brinkmann, Sandra Ciesek, Thomas Czypionka, Isabella Eckerle, Giulia Giordano, Claudia Hanson, Zdenek Hel, Pirta Hotulainen, Peter Klimek, Armin Nassehi, Andreas Peichl, Matjaz Perc, Elena Petelos, Barbara Prainsack, Ewa Szczurek. An action plan for pan-European defence against new SARS-CoV-2 variants. *Lancet.* 2021 6-12 February; 397 (10273): 469-470.
- 25) Nathan D. Grubaugh, Emma B Hodcroft, Joseph R Fauver, Alexandra L Phelan, Muge Cevik. Public health actions to control new SARS-CoV-2 variants. *Cell.* 2021; 184 (5): 1127-1132.
- 26) Rochelle P Walensky, Henry T Walke, Anthony S Fauci. SARS-CoV-2 Variants of Concern in the United States- Challenges and Opportunities. *JAMA.* 2021; 325 (11): 1037-1038.
- 27) Kathleen M Neuzil. Interplay between Emerging SARS-CoV-2 Variants and Pandemic Control. *N Engl J Med.* 2021; 384 (20): 1952-1954.
- 28) Zaixing Jia, Wenping Gong. Will Mutations in the Spike Protein of SARS-CoV-2 Lead to the Failure of COVID-19 Vaccines? *J Korean Med Sci.* 2021; 36 (18): e124.