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International Journal of Infectious Diseases 116 (2022) 271–272

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

A CLUSTER OF SARS-COV-2 DELTA VARIANT OF CONCERN ADDITIONALLY HARBORING F490S, NORTHERN LOMBARDY, ITALY

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ARTICLE INFO

Article history:
Received 6 October 2021
Revised 29 November 2021
Accepted 23 December 2021

Keywords:
SARS-CoV-2
COVID-19
variant of concern
Delta
B.1.617.2
F490S

ABSTRACT

The Delta variant of concern (VOC) of SARS-CoV-2 has become dominant worldwide. In this article, we report a cluster caused by B.1.617.2 harboring the additional mutation of concern (MOC) F490S. We observed that 5 fully vaccinated subjects aged between 47 and 84 years were infected with this variant. The immune escape mutation F490S, first identified in the Lambda VOI, appears to impair vaccine efficacy and is rapidly increasing in prevalence worldwide.

Dear Editor,

Since the beginning of 2021, a SARS-CoV-2 lineage originally described in India has become the predominant circulating variant of the COVID-19 pandemic. This variant of concern (VOC) was renamed as “Delta” by the World Health Organization (WHO), VOC-21APR-02 by Public Health England, 21A/S:478K by NextStrain, and G/452R.V3 by GISAID. The most refined nomenclature has been proposed by PANGOlin, which recognizes sublineages ranging from AY.1 to AY.117. T478K and L452R are the main mutations of concern (MOC) within the Spike protein of Delta.

In this article, we report a cluster of B.1.617.2 + F490S occurring in 2 families living in the same small town in Northern Lombardy. All cases were first tested by real-time reverse transcription–polymerase chain reaction (RT-PCR) and, if positive, sequenced by next-generation sequencing (NGS) as previously reported (Liu Z et al., 2021).

Overall, the cluster was of 6 subjects who tested SARS-CoV-2 RNA positive between September 6 and 7, 2021. On September 6, 2021, an 84-year-old immunocompetent male (fully vaccinated with BNT162b2 on March 1 and 22, 2021) tested SARS-COV-2 positive at a surveillance nasopharyngeal swab (NPS) at hospitalization for vascular surgery (cycle threshold [Ct] 27 and 28 for ORF1ab and N genes, respectively; ELITe MGB kit, ELITechGroup, Turin, Italy). He always remained fully asymptomatic. On September 7, 2021, his 53-year-old daughter (fully vaccinated with BNT162b2 on February 9, 2021, and March 2, 2021) also tested SARS-CoV-2 positive with polymerase chain reaction (PCR) (Ct 24 and 22 for ORF1ab and N genes, respectively). Ageusia was the only clinical sign she developed. On the same day, both her 55-year-old husband (fully vaccinated with Ad26.COV2.S on June 2021) and her 16-year-old son (vaccinated with a single dose of messenger RNA [mRNA]-1273 on September 6, 2021) resulted real-time PCR positive (Ct 20 and 18 for ORF1ab and N genes, respectively, and Ct 18 and 17 for ORF1ab and N genes, respectively; ELITe MGB kit). None of them needed hospital admission; only the husband was symptomatic with fatigue and fever.

On September 6, 2021, 2 more unrelated individuals from the same village, a 57-year-old male and his 47-year-old wife, tested NPS virus–positive. Eight days before, they had gone a 3-hour car trip together with 3 of the 4 previously mentioned patients. Both had been fully vaccinated with Ad26.COV2.S on June 1, 2021. The wife developed fever, ageusia, and anosmia for just 1 day, whereas the husband remained asymptomatic (Table 1).

Abbreviations: VOC, variant of concern; MOC, mutation of concern.

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https://doi.org/10.1016/j.ijid.2021.12.362

Case ID	Age	Gender	Date of positivity	Vaccinal status	PCR	Symptoms	
1	84	M	Sep 6, 2021	BNT162b2 (March 2021)	Ct 27 (ORF1ab) Ct 28 (N)	Asymptomatic	
2	53	F	Sep 7, 2021	BNT162b2 (March 2021)	Ct 24 (ORF1ab) Ct 22 (N)	Ageusia	Daughter of case 1
3	55	M	Sep 7, 2021	Ad26.COV2.S (June 2021)	Ct 20 (ORF1ab) Ct 18 (N)	Fatigue and fever	Husband of case 2
4	16	M	Sep 7, 2021	Single dose mRNA-1273 (Sep 2021)	Ct 18 (ORF1ab) Ct 17 (N)	Asymptomatic	Son of cases 2 and 3
5	57	M	Sep 6, 2021	Ad26.COV2.S (June 2021)	Ct 24 (ORF1ab) Ct 25 (N)	Asymptomatic	Eight days before, car trip with aforementioned patients
6	47	F	Sep 6, 2021	Ad26.COV2.S (June 2021)	Ct 22 (ORF1ab) Ct 23 (N)	Fever, ageusia, anosmia	Wife of case 5 Eight days before, car trip with aforementioned patients

NGS analysis of the 6 SARS-CoV-2 strains revealed B.1.617.2 additionally harboring F490S mutation. All the sequences obtained in the study have been deposited in GISAID (accession numbers EPI_ISL_4312406-4312861-4313301-4313638-4314142-4314645).

F490S is the hallmark MOC of VOIs Lambda (C.37) and is also found at frequencies higher than 50% in Q.5 and B.1.1.456 lineages. F490 is an *O*-linked glycan site; F490S causes resistance to convalescent sera (Liu Z et al., 2021) and escape to several monoclonal antibodies (mAbs) (such as C121 but not C135 and C144) (Weisblum Y et al, 2020) and nanobodies (Koenig P-A et al., 2021). It was also reported in a patient with B-cell chronic lymphocytic leukemia who was treated with convalescent plasma (Monrad I et al., 2021). It has also been occasionally reported in all the other VOCs, remaining largely sporadic (except for Alpha (Grabowski et al., 2021), where it accounted for 0.4% before the advent of Delta). As of September 10, 2021, GISAID reported F490S in 30 of 418,956 B.1.617.2 sequences, in 1 of 24,391 AY.3 sequences, in 2 of 2,926 AY.3.1 sequences, in 18 of AY.4 325,042 sequences, in 4 of 40,191 AY.12 sequences, and in 1 of 9,447 AY.20 sequences. F490S had never been reported in Delta sequences in Italy before, but its frequency is increasing worldwide since the beginning of September 2021 (http://outbreak.info/situation-reports), recommending close monitoring and further investigations of vaccine efficacy.

We declare that we have no conflict of interest related to this manuscript.

“This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.”

SARS-CoV-2 reverse transcription–polymerase chain reaction and sequencing were performed according to the surveillance program of the Italian National Institute of Health and Ministry of Health.

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