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**Highlights**

- The Delta variant of concern of SARS-CoV-2 has become dominant worldwide
- We report a cluster caused by B.1.617.2 harboring the additional mutation of concern F490S
- The immune escape mutation F490S appears to impair vaccine efficacy
- The immune escape mutation F490S is rapidly increasing in prevalence worldwide

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

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**Abstract**

The Delta variant of concern (VOC) of SARS-CoV-2 has become dominant worldwide. We report here a cluster caused by B.1.617.2 harboring the additional mutation of concern (MOC) F490S. Infection occurred in 5 fully vaccinated subjects between the ages of 47 and 84. The immune escape mutation F490S, first identified in the Lambda VOI, appears to impair vaccine efficacy and is rapidly increasing in prevalence worldwide.

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

**Abbreviations**: VOC: variant of concern; MOC: mutation of concern

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. Such variant of concern (VOC) was renamed “Delta” by 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.

We report here a cluster of B.1.617.2 + F490S occurring in two families living in the same small town in Northern Lombardy. All cases were first tested by real-time RT-PCR, and, if positive, sequenced by 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-years-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-years old daughter (fully vaccinated with BNT162b2 on February 9, and March 2, 2021) also tested SARS-CoV-2 positive with 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-years old husband (fully vaccinated with Ad26.COV2.S on June 2021) and her 16-years old son (vaccinated with a single dose of mRNA-1273 on September 6, 2021) resulted real-time PCR positive (Ct 20 and 18, 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, two more unrelated individuals from the same village, a 57-years old male and his 47-years old wife tested NPS virus-positive. Eight days before, they had done a 3-hour car trip together with 3 of the 4 above-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, while the husband remained asymptomatic (Table 1).

NGS analysis of the six 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 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 B-cell chronic lymphocytic leukemia patient 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 out of 418,956 B.1.617.2 sequences, in 1 out of 24,391 AY.3 sequences, in 2 out of 2,926 AY.3.1 sequences, in 18 out of AY.4 325,042 sequences, in 4 out of 40,191 AY.12 sequences, and in 1 out 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.

| 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 together with above-mentioned 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 together with above-mentioned patients |

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