Hôpitaux Universitaires Genève

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Geneva, November 10, 2021

N/réf : PV/LK

Geneva Centre for Emerging Viral Diseases

Division of Infectious Diseases

Department of Medicine

Laboratory of virology

Division of Laboratory Medicine

Diagnostic Department

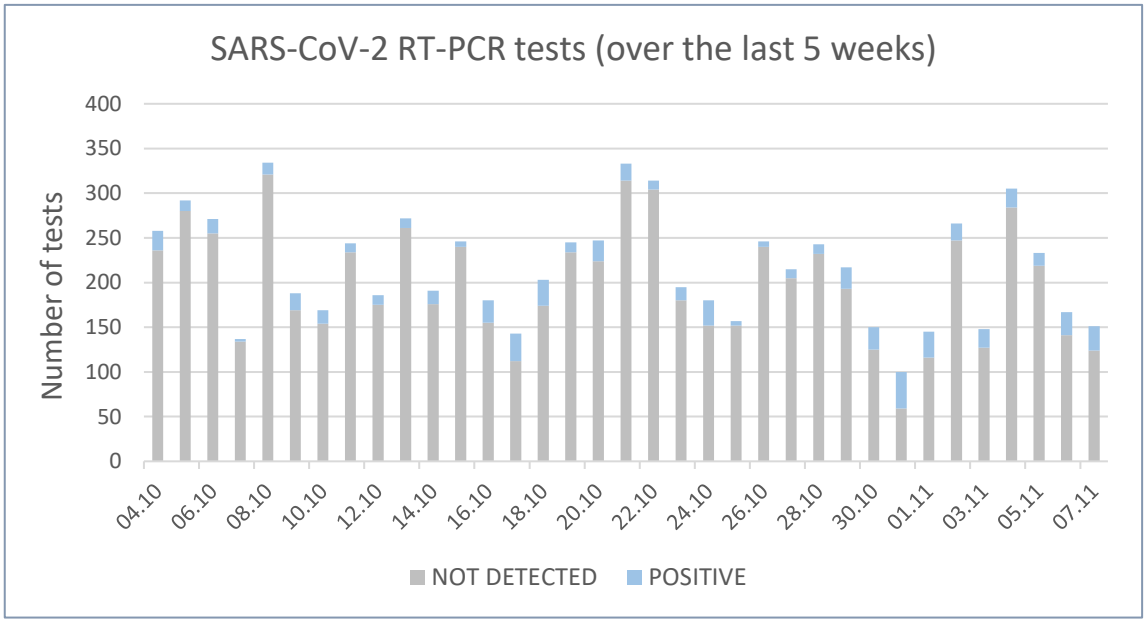
SARS-CoV-2 genomic and variants surveillance in Geneva: weekly update
Focus on E484Q containing sub-lineages

The laboratory of virology of the Geneva University Hospitals as a sentinel site for the Geneva area

The number of tests (PCR and antigen tests) performed at the laboratory of virology of the Geneva University Hospitals represents around 18% of the total number of tests performed in the canton of Geneva during week 44 (2412/13557). Roughly 30% of the positive specimens collected in the Geneva area were processed at HUG (175/586) during week 44. Tests performed at our outpatient testing center (located in the Hospital but open to anyone from the community) are either PCR-based or antigen-based. Most symptomatic patients are screened by RT-PCR and all positive antigen-based tests are confirmed by PCR, allowing screening for variants.

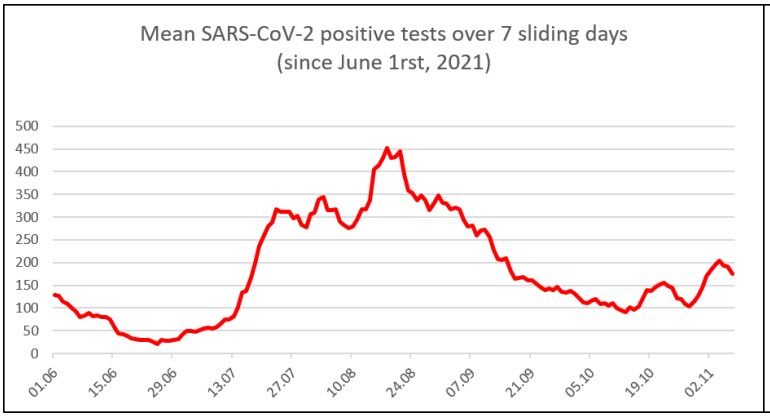
WGS is carried out in close collaboration with the Health 2030 Genome Center in Geneva and Philippe Le Mercier from the Swiss Institute of Bioinformatics. Since March 1, 2021, the sequencing has been done within the Swiss national SARS-CoV-2 genomic and variants surveillance program. All specimens with a Ct value ≤32 are sequenced. In some instances, sequencing can be done on specimens sent by other laboratories in Switzerland. Phylogenetic analysis data are produced by Nextstrain, in collaboration with Richard Neher's group at the University of Basel. The number of positive tests in the canton and the total number of tests done during the surveilled week come from the website of the Direction Générale de la Santé in Geneva (available at https://infocovid.smc.unige.ch/), accessed November 8, at 18:00 pm.

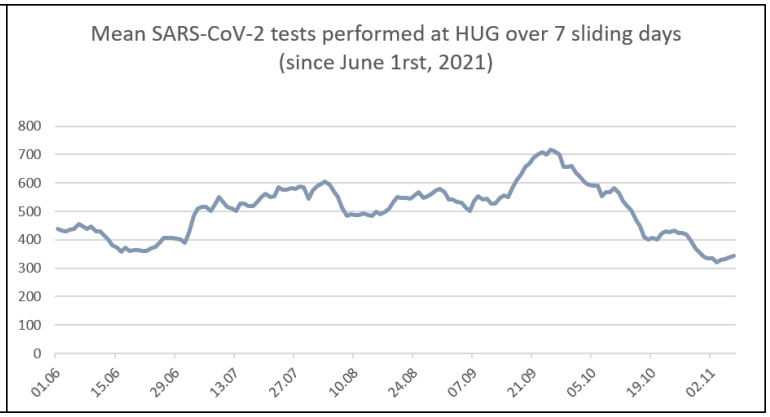
This report has been produced in collaboration with the Geneva Cantonal Physician team, in order to produce extensive information regarding transmission chains and epidemiological links between SARS-CoV-2-positive individuals displaying the E484Q mutation.



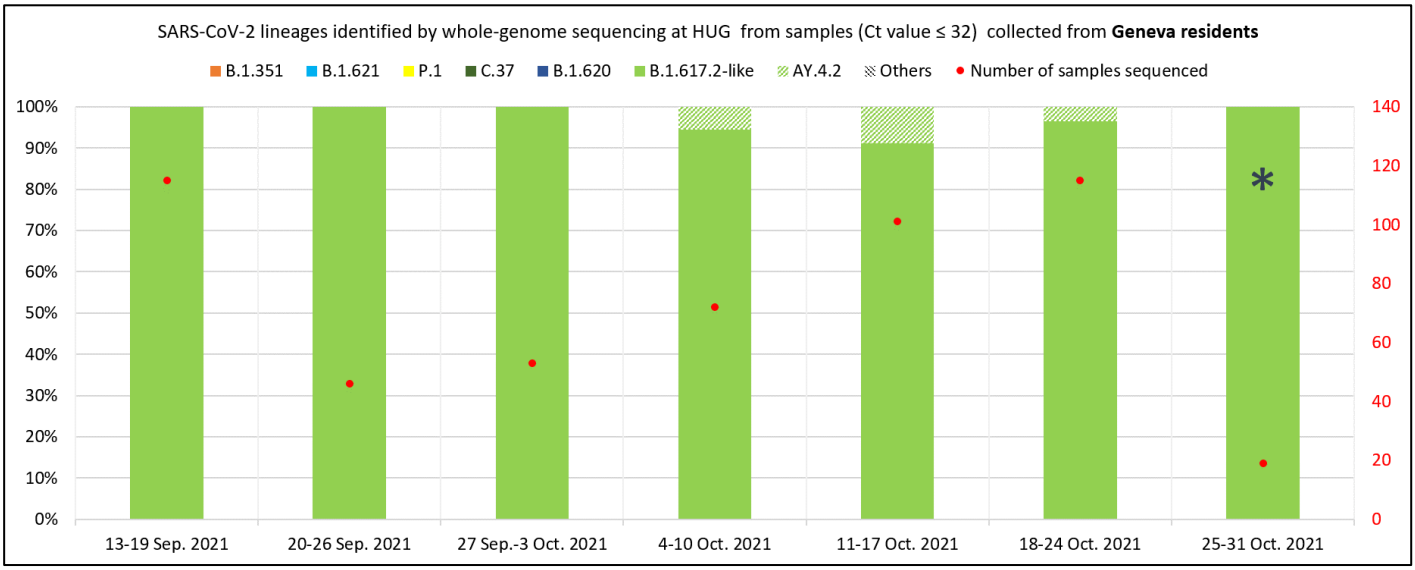
During week 44, the absolute number of positive SARS-CoV-2 tests continued to increase, and the mean positivity rate over 7 sliding days reached 9%.

Similarly, at our outpatient symptomatic testing center (sector E'), the mean positivity rate continued to increase during week 44, and was 20% on average for the whole week.





SARS-CoV-2 lineages identified by whole-genome sequencing at HUG from samples (Ct value ≤32) collected from Geneva residents



Results of WGS of 582 sequences submitted to GISAID between September 13 and October 21, 2021.

Note: due to a technical problem encountered during the WGS process, a total of 76 SARS-CoV-2 positive samples collected between September 23 and 28 could not be sequenced. This partly explains the drop in the number of sequences available during this period.

*Partial data for week 43 (October 25 to October 31), as sequencing is still ongoing. Numbers will be updated in the next report.

Exclusively B.1.617.2 (Delta, or one of its sub-lineages) sequences have been identified in samples collected from Geneva residents since mid-September.

Three new sequences of the Delta sub-lineage AY.4.2 (a Variant under Investigation/Variant under Monitoring) **have been identified in the last sequencing batch**. In total, the Delta sub-lineage AY.4.2 represented 5.5% (4/72), 9% (9/101) and 4% (5/115) of the sequences collected during weeks 40, 41 and 42, respectively (from October 4 to October 26). One was retrieved from a hospitalized patient repatriated from abroad. Of note, preliminary observational data from the UK, where this sub-lineage is increasing in proportion, do not indicate that there is more severe disease after infection with this specific variant.

In parallel, **since the beginning of October, 19 sequences of Delta additionally carrying the 484Q mutation have been identified in the Geneva area, collected between 7 and 24 October.** This mutation has been implicated in immune escape and warrants further surveillance.

Among those, **12/19 (63%) were retrieved from post-vaccination infections**, and 2 from children (age between 10 to 15).

Of those 19 samples with the 484Q mutation collected from October 14 to 24, **18 of them include two additional mutations on the spike gene:** one mutation in the furin cleavage site (V687I) and one outside of the RBD and furin cleavage site (T859N).

- Among those mutations, E484Q (located in the RBD) is known to decrease neutralization from convalescent, vaccinated sera and the monoclonal antibody casirivimab used in clinical practice; however, previously published data originating from *in vitro* pseudoneutralization studies also indicated that its presence doesn't seem to have a substantial effect in combination the 452R mutation carried by the Delta sub-lineage. Similarly, the studies using pseudovirus do not suggest that the E484Q mutation, in combination with the L452R mutation, enhances cell entry or infection.

- The other 2 mutations are not known to have immune escape properties, nor to lead to increased infectivity. However, the presence of one mutation in the furin cleavage site warrants further surveillance, as similar mutations are associated with increased transmissibility.

The combination of those 3 mutations seems to be specific to Switzerland and has previously not been identified elsewhere. Their combined effect remains unknown. Of note, the presence of the E484Q mutation on the Delta background was already observed in the B.1.617.1 Kappa and B.1.617.3 variants, which were both replaced by Delta B.1.617.2. It is worth noting that the E484Q mutation in B.1.617.2 appears to be a reversion to the ancestral state shared with B.1.617.1 and B.1.617.3.

According to the cantonal physician team, five cases have been linked together during a large event which required the COVID certificate. This may partially explain the large proportion of vaccinated individuals infected by this specific variant. Among other cases, some were related (through family links or social events).However, **all transmission chains could not be retraced** and only one of these cases was imported, **indicating possible community transmission.**

In addition, one sequence carrying the E484Q mutation also includes the additional spike mutation at position V1104L. This combination has been observed previously in multiple places but at low frequency. According to the cantonal physician team, this virus is linked to vaccinated travelers returning from India. No similar sequence has been retrieved since October 7.

None of them are currently or have been hospitalized because of COVID-19 at Geneva University Hospitals since the beginning of October. Of note, no further data is available regarding the health status of those individuals or their risk factors for severe disease.

Post-vaccination infections in the canton of Geneva

Post-vaccination infection is defined here as a positive SARS-CoV-2 test occurring more than 14 days after the second vaccine dose. This surveillance is done in collaboration with the Direction Générale de la Santé (DGS) of Geneva. Data are collected by the DGS of Geneva during contact tracing calls after having obtained informed consent from SARS-CoV-2 positive patients. The list of patients with post-vaccination infections is sent weekly to HUG virology laboratory, which makes an effort to retrieve initial diagnostic samples in order to ensure sequencing, as recommended by FOPH.

Among the 599 new COVID-19 cases reported by the Direction Générale de la Santé in Geneva over week 44, 167 (28%) have been identified as post-vaccination infections.

Documented infections with AY.4.2 predominantly were retrieved in vaccinated individuals > 50% (10/19).
Similarly, 63% (12/19) of documented infections with a sequence carrying the E484Q mutation were identified in previously vaccinated individuals.

Whether these proportions are high because of immune escape properties of the variants or because of specific behavioral events and exposure bias (see above) remains uncertain. Of note, preliminary observational data from the UK seem to suggest that additional mutations carried by AY.4.2 do not lead to additional vaccine escape. No data is available so far regarding possible immune escape of the Delta sub-lineages with additional 484Q, V687I and T859N mutations. More information is expected to follow in the next weeks.

Conclusions

- Both the absolute number of positive tests and the mean positivity rate continued to increase during the last week.

- The majority of new SARS-CoV-2 cases still arose in unvaccinated individuals, with Delta or one of its sub-lineage being the only identified variant in the Geneva area since mid-September.

- Three new sequences of the “variant under monitoring/investigation” Delta sub-lineage AY.4.2 have been retrieved in the last sequencing batch. However, no positive sample was identified after week 42.

- 18 Delta sub-lineage sequences carrying 3 additional Spike mutations, including the E484Q mutation, known to lead to immune escape, have been identified in the Geneva area since October 14, in the last 2 sequencing batches. Most have been retrieved in previously fully vaccinated individuals. Of note, because of the low numbers, no conclusion can be drawn at this time. Five cases have been linked together during a large event which required the COVID pass, one has been imported; however not all transmission chains could be retraced, indicating possible community transmission.

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