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Geneva Centre for Emerging Viral Diseases

Division of Infectious Diseases

Department of Medicine

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Division of Laboratory Medicine

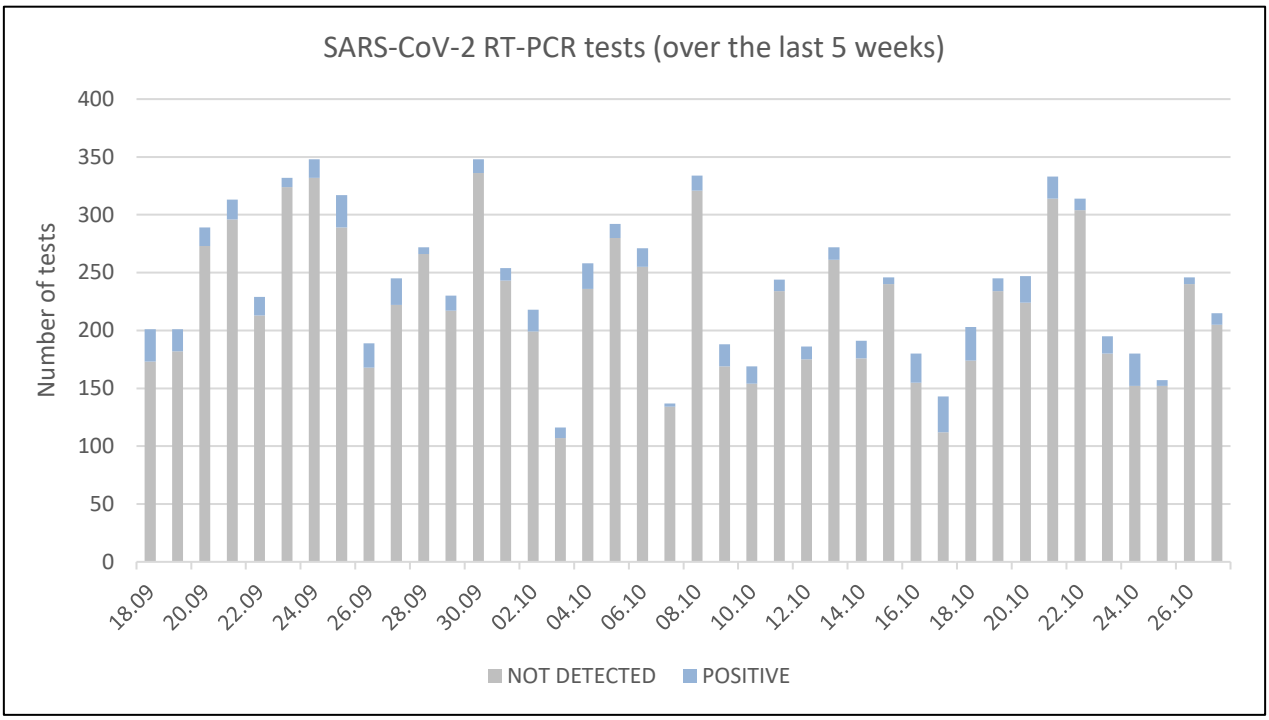
Diagnostic Department

SARS-CoV-2 genomic and variants surveillance in Geneva: weekly update
With a focus on AY.4.2

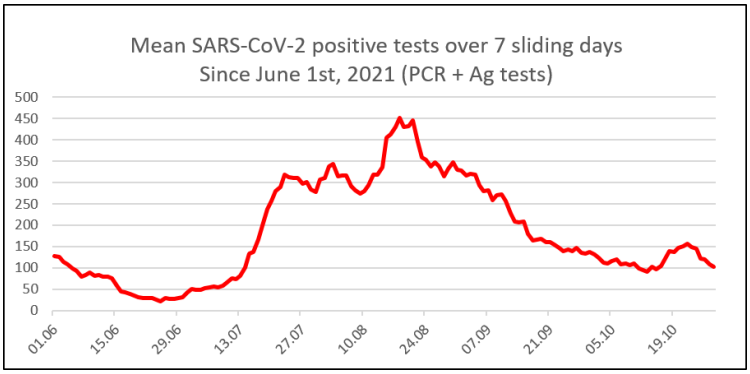
The laboratory of virology of the Geneva University Hospitals as a sentinel site for the Geneva area

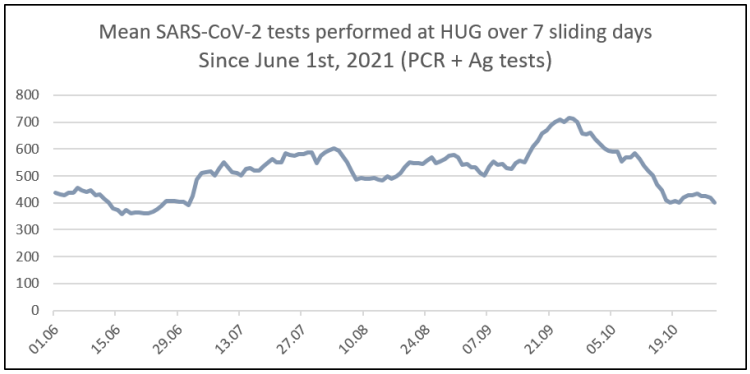
The number of tests (PCR and antigen tests) performed at the laboratory of virology of the Geneva University Hospitals represents around 18% of the total number of tests performed in the canton of Geneva during week 42 (3032/17546). Roughly 30% of the positive specimens collected in the Geneva area were processed at HUG (145/500) during week 42. 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 October 28, at 10:00 am.

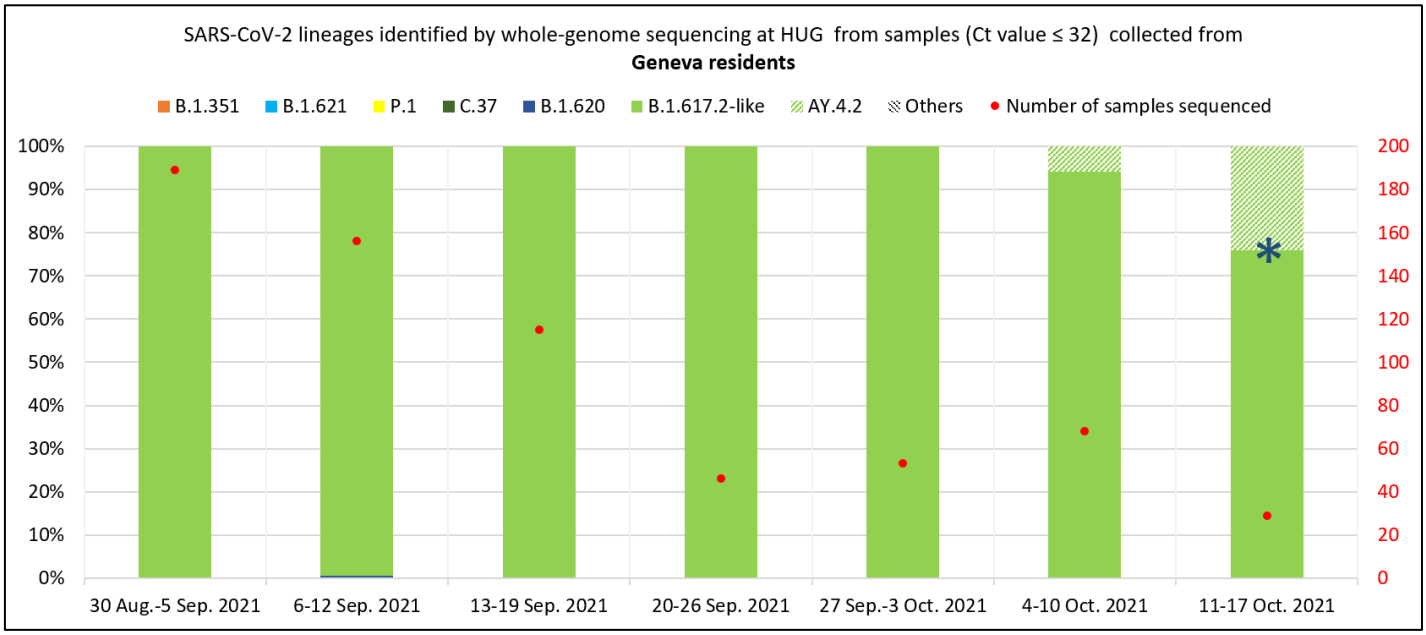


During week 42, both the absolute number of positive SARS-CoV-2 tests and the percentage of positive results progressively decreased since the last peak at the end of week 41.
Similarly, at our outpatient symptomatic testing center (sector E'), the mean positivity rate during week 42 decreased to around 15%.





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



Results of WGS of 656 sequences submitted to GISAID between August 30 and October 15, 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 42 (October 11 to October 17), as sequencing is still ongoing. Numbers will be updated in the next report.

All but one sequences retrieved in samples collected from Geneva residents since the beginning of September were identified as B.1.617.2 (Delta, or one of its sub-lineages). One B.1.620 sequence was collected at the beginning of September, and this lineage has never been identified thereafter.

Mutations can accumulate in the Delta background, and numerous Delta sub-lineages (not all depicted here), have been identified.

Mid-October, one Delta sub-lineage called AY.4.2, has been designated as a *Variant Under Monitoring* (not yet a Variant of Concern (VOC) or a Variant of Interest (VOI)) by both the ECDC and Public Health England, because of a slowly increasing proportion of cases in various countries, particularly the UK, although its spread outside UK is less consistent. In the UK, its estimated transmission advantage seems to be between 10 and 15%, although it is less clear in other countries where the sub-variant is less frequent, due to a small dataset. It is too soon however to conclude if this indicates an intrinsically higher transmissibility or increased spread led by behavioral events.

This AY 4.2 Delta sub-lineage carries, among others, 3 additional mutations in the Delta background: 2 on the spike gene: Y145H, A222V and one on ORF1ab gene: 2529V. The Y145H mutation was also observed sporadically in Alpha but never spread. In EU1, A222V did not appear to have a major effect as assessed by monoclonal antibody binding or pseudo-typed virus titers. It appeared repeatedly in larger clades and might convey a slight advantage or have a stabilizing/permissive effect. Both mutations are in the N-terminal region, which is the second most dominant antigenic epitope after the RBD. No data suggests that they affect neutralization of this strain. However, more data are needed, and more information will follow.

In Geneva, this sub-lineage had only been identified once during the summer, in late July, in an individual that experienced a breakthrough SARS-CoV-2 infection. **In the last sequencing batch** however**, this variant was identified in 11 (14%) of the 78 samples collected between October 6 and October 13 that have been sequenced (here depicted in dotted green)**.

According to the cantonal physician team, those cases identified in Geneva are not all part of the same cluster. 2 were retrieved from returning travelers, 6 cases were observed in 2 familial clusters not linked to a previously known transmission chain, and all remaining infections were isolated and not linked together. **Those observations are early signals that there is already community transmission of AY 4.2 in the Geneva area**.

More than half of those infections (7/11) were identified as post-vaccination breakthrough infections by the cantonal physician team (occurring > 14 days after second vaccination in fully vaccinated individuals), with a delay ranging from 99 to 206 days between the sampling and the last vaccine dose.

None of them are currently or have been hospitalized because of COVID 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.

Of note, those numbers are too low to draw any solid conclusion on transmissibility and/or vaccine escape. More information will follow in the next reports regarding any potential increased risk associated with Delta sub-lineages.

Additional technical remark on sequencing: A potential issue in amplification of a genomic region of SARS-CoV-2 due to the specifics of the usual protocols used in sequencing has been identified, and may result in the misclassification of Delta sub-lineages. However, characteristics mutations of the AY 4.2 variants are located outside of this region. Thus, identification of AY 4.2 should not be affected.

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 508 new COVID-19 cases reported by the Direction Générale de la Santé in Geneva over week 42, 118 (23%) have been identified as post-vaccination infections.

Despite the delay required to obtain samples tested by other laboratories, and the technical delay inherent to sequencing, results are already available for 43 (25%) of the 169 sequences identified as post-vaccination infections and collected between October 1 and October 15, 2021. Over the same time period, the Direction Générale de la Santé declared a total of 719 new COVID-19 cases.
7 (16%) of the 43 available sequences originating from people infected after vaccination were AY 4.2.

Those numbers are too low to draw any solid conclusion on transmissibility and/or vaccine escape and should not be over-interpreted. More information will follow in the next reports regarding any potential increased risk associated with Delta sub-lineages.

Conclusions

- Both the absolute number of positive SARS-CoV-2 tests and the percentage of positive results progressively decreased. Note however that the mean positivity rate during week 42 in our outpatient symptomatic testing center was still around 15%.

- As usual, the majority of new SARS-CoV-2 cases arose in unvaccinated individuals.

- Delta (or one of its sub-lineages) has continued to be the sole SARS-CoV-2 variant identified among sequences collected from Geneva residents, with no other VOC/VOI sequences retrieved in the Geneva area over the surveilled period.

- The recently designated "*Variant under Monitoring*" Delta sub-lineage AY.4.2 was identified in 11 (14%) of the 78 sequences available in the last sequencing batch, collected at the beginning of October (before that, only one sequence had been recovered in the Geneva area in late July 2021). Those cases are not all part from the same cluster, and only 2 were retrieved from returning travelers, according to the Cantonal Physician team. This is a new early signal of a community transmission of this variant. Some cases were identified as post-vaccination infections. Of note, because of the low numbers, no conclusion can be drawn at this time, and more information will follow.

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