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Swiss national SARS-CoV-2 genomic and variants surveillance program: report of the month of October

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1. Summary

Nearly 18% of the total number of cases identified in Switzerland were sequenced by the Surveillance program, yielding over 5917 sequences in October.

In October, COVID-19 cases numbers increased in Switzerland, and were due almost exclusively to the B.1.617.2 (Delta) variant or its sub-lineages.

Circulation of all other variants has essentially stopped, with only 2 non-Delta lineages being identified (B.1.640 and B.1.318). Out of approximately 7000 sequenced samples, 13 could not be assigned to a lineage due to poor sequencing results.

Additional mutations continue to accumulate in the Delta. A large variety of sub-lineages have already been observed, with few data available regarding any additional relevant properties, and no strong sign in Switzerland of any specific variant outcompeting others.

The AY.4.2 sub-lineage, considered a Variant Under Monitoring by both the ECDC and Public Health England, has increased in proportion, but still only accounts for 0.6-0.7% of sequences retrieved during the month of October.

A number of other interesting mutations have been identified, primarily lineages with mutations at the position 484 of the spike protein, as well as a novel mutation in the Furin cleavage site.

No important geographical breakdown of a particular sub-lineage has been noticed.

Unsurprisingly, B.1.617.2 (Delta or its sub-lineages) was also the most frequent variant detected in wastewater during the month of October.

As this report was being finalized (in November), a new variant of concern named Omicron (B.1.1.529) with the most spike mutations ever seen was detected first in southern Africa. It is too soon to know if it can outcompete Delta. More information will be gathered on its immune escape and transmission properties. Preliminary results show that it is still detected by RT-PCR tests, but with S-gene target failure that can be used as a proxy for it prior to sequencing, as seen with VOC Alpha. A probable case returning from South Africa was announced by the FOPH on 28.11.

2. Description of the Swiss national SARS-CoV-2 genomic and variants surveillance program.

The overall goal of the program is to provide epidemiological trends and to highlight meaningful observations.

Because greater transmissibility and/or immune escape potential of the different VOCs and VOIs can result in new surges in COVID-19 numbers despite the vaccination campaign, this program aims to closely monitor each variant displaying mutations known to be linked with either increased transmissibility or immune escape potential.

Currently, 15 diagnostic laboratories have joined the program, including university hospital centres in Switzerland (Geneva, Lausanne, Bern, Basel, Zurich, St-Gall, Ticino), in addition to private laboratories (Viollier; Medisupport including Dianalabs, Polyanalytic, Dianalabs Valais, Proxilab and Bioanalytica ; Biolytix; Synlab Bioggio (TI); Labor Team W, Risch), cantonal-based laboratories (Hôpital du Valais – Institut Central), Spital Region Oberaargau (Bern, Solothurn, Aargau, Luzern), and 3 high-throughput sequencing platforms (Health 2030 Genome Centre in Geneva, Functional Genomics Centre Zurich run by ETH Zürich and University of Zürich, Genomics Facility Basel run by ETH Zürich and University of Basel).

Processed sequencing data are shared openly within 14 days from positive PCR result through the GISAID platform (https://www.gisaid.org) and eventually through the Swiss Pathogen Surveillance Platform (SPSP). The centralized analysis of this National Surveillance will be performed by the groups of Pr. Neher, Pr. Stadler and Dr. Althaus, where variants of concern are counted, analyzed and all sequences scanned for new variants with potential changes in antibody-Spike interactions (https://nextstrain.org/groups/swiss, https://covariants.org/per-country, https://cov-spectrum.ethz.ch). This work is done in close collaboration with the Swiss National COVID-19 Science Task Force and the Swiss Institute of Bioinformatics (SIB).

In order to complement the genomic surveillance based on patient samples, sequencing of SARS-CoV-2 in wastewater samples is also performed, initially funded for 6 months. Samples are collected daily in six wastewater treatment plants (WWTP), under the coordination of Eawag. Up to 50 samples per week over the first 26 weeks have been performed. The sequencing and analysis of these samples, including detection of variants, is done under the coordination of Prof Niko Beerenwinkel. It started in December 2020 for Lausanne and Zurich, and in February 2021 for all six WWTP (https://bsse.ethz.ch/cbg/research/computational-virology/sarscov2-variants-wastewater-surveillance.html). The analysis of wastewater samples is envisaged to run until the end of the surveillance program on 31.3.2022.

Immunological characterization of the variants within the surveillance program is coordinated by Professor Trono's team at EPFL.

This report has been produced by Marc Friedli, Pauline Vetter, Samuel Cordey, Erik Boehm, Richard Neher, Christian Althaus, Martina Reichmuth, Cornelius Römer, Niko Beerenwinkel, David Dreifuss, Chaoran Chen, Tanja Stadler, Priscilla Turelli, Didier Trono, Emma Hodcroft, Nadja Wipf, Damir Perisa, and Laurent Kaiser. The list of the participants and collaborators of the program can be found at the end of this report in the appendix.

This report covers the period of October 4 to October 31 (weeks 40, 41, 42, 43). All data presented in this report are based on the sampling date.

3. Variants of concern (VOCs), variant of interest (VOI) and other surveilled variants: brief summary and special focus

Four variants and their sub-lineages are still considered VOCs by the WHO, B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), and B.1.617.2 (Delta). While still a VOC for WHO, the European Centre for Disease Prevention and Control de-escalated Alpha as a VOC.

The Delta sub-lineage AY.4.2, considered a Variant under monitoring by both the ECDC and Public Health England, continues to slowly increase in proportion of cases in various European countries. Its estimated transmission advantage is between 10 and 15%, although this is still unclear due to a small dataset outside of the UK. Within the UK, no difference in hospitalization rate or severity has been noted, nor have any additional immune escape concerns been identified. Of note, preliminary observational data from the UK suggest no significant reduction in vaccine effectiveness against AY.4.2 compared to the original B.1.617.2 variant. For detailed characteristics of the mutations carried by the AY.4.2 sub-lineage, please refer to the report from the month of September.

Other spike mutations spotted across various Delta sub-lineages include:

- K417N: This mutation arose independently within lineages AY.1 and AY.2, but these lineages have decreased in frequency since their first identification. Notably, position 417 is mutated in VOCs Beta (to `N`) and Gamma (to `T`) and has been associated with reduced neutralization in some subjects.
- Q613H: This mutation arose independently several times in Delta. Growth signals that were initially present in the data have weakened and it is hence unclear whether it has a consistent growth advantage across countries. Notably, it is adjacent to the D614G mutation that became dominant early in the pandemic.
- E484Q/A: The E484Q mutation was ancestral to B.1.617.2 (Delta), and is found in the sister lineages B.1.617.1 and B.1.617.3. Recently it has begun re-appearing in Delta. Mutations to K or Q at position 484 are often associated with escape from some monoclonal antibodies and reduced neutralization by vaccine sera. In vitro studies suggest that the effect of 484K/Q mutations, in the presence of the L452R mutation (found in Delta), have little effect. The effect of a 484A mutation is unclear at this time.
- V687I: This mutation occurs in the Furin cleavage site. Nearby mutations at position 681 have been found in VOCs (Alpha and Delta), and various VOIs, and are believed to increase transmissibility through improved cleavage. Whether V687I has a similar effect is still unknown

A new variant, B.1.640, was recently identified in Europe with a novel mutation set: 9 deleted amino acids and 12 amino acid mutations (not including the ubiquitous D614G). Many of these mutations occur in: the N-terminus (associated with immune escape), the RBD (associated with immune escape and altered transmissibility), and at the Furin cleavage site (associated with increased transmissibility). Currently only 5 sequences (1 in Switzerland) have been identified. While this lineage is not apparently spreading well, its mutation set deserves further scrutiny.

On the day of completion of this report, a new B.1.1.529 variant of concern (Omicron) has been identified in South-Africa and travelers from South Africa in other countries, carrying an unprecedented number of mutations on the Spike protein, both with immune escape and/or increased transmissibility properties. This variant has not yet been confirmed to be in Switzerland, although there is a preliminary report of it being detected in a traveler from abroad; its spread will be scrutinized closely over the next weeks.

Note: The Health 2030 Genome Center highlighted a potential issue in a genomic region of the SARS-CoV-2, which may lead to a misclassification of Delta sub-lineages AY*. Characteristic mutations of the AY 4.2

mutations are located outside of the amplification primer, and this issue should not affect the identification of AY 4.2.

Vaccines effectiveness:
In large populations, protection against severe disease seems to be maintained against the Delta variant, although complete protection against infection is not. However, this protection in specific populations such as the elderly shows signs of decreasing over time, which justified the approval of a booster dose in this specific population.
While the viral shedding in vaccine-breakthrough infections caused by the Delta variant seems to be shortened, data regarding the length of infectiousness and transmissibility are still scarce and conflicting.

Therapeutic effectiveness
Numerous mutations have been reported to substantially reduce the therapeutic effectiveness of mAbs currently used to treat COVID-19, as well as those under development (Table 1). Notably, the Delta variant retains susceptibility to all mAbs approved for use in Switzerland. Delta is resistant to Bamlanivimab (not in use in CH), and displays weak resistance to Imdevimab, but the combination of Imdevimab and Casirivimab (which is the standard combination) remains highly effective *in vitro*. Delta sub-lineages with the K417N mutation are resistant to Casirivimab, but the combination of Imdevimab and Casirivimab still remains highly effective.

Some point mutations may annihilate the *in vitro* neutralizing effect of the sotrovimab.

AA position	CAS	IMD	CAS&IMD	SOT
337		*L*		R/L/H/T
340				K/A/G
356				T
406	*D/W*	*W*	*W*	
417	*E/N/R*			
439		*K/V*		
440		*K*		
444		*N/Q/T/L/M/x*	*T*	
445	*T*	*A*	*A*	
446		*V/x*		
450		*D*		
453	*F*			
455	*F*			
476	*S*		*D (weak, 4 fold)*	
484	*K/Q*			
485	*D*			
486	*V/L/S/X*			
493	*K/E/R*	*R*		
494	*P*			
498		*H*		
499		*S*		

Table 1: resistance mutations to mAbs used to treat COVID-19 in Switzerland causing 5 fold or greater reduction in neutralization, except for 476 D which causes only a weaker 4 fold reduction. CAS = Casirivimab, IMD = Imdevimab, SOT = sotrovimab

In addition to mAbs, there are a number of other antiviral treatments under development, such as protease inhibitors (either targeting host cell proteases such as TMPRSS2, or virally encoded ones such as 3CL like proteases) like Paxlovid® (PF-07321332) or RNA nucleotide analogues (which interfere with replication of the viral genome such as Molnupiravir). No data is available regarding mutations enabling escape from these proteases (and there are unlikely to be any for treatments targeting host cell proteases). In contrast, serial passage of virus in the presence of Molnupiravir lead to the accumulation of mutations that increased viral resistance to Molnupiravir. Despite this, the mutations conferring

resistance to Molnupiravir significantly reduced overall viral fitness, and were thus detrimental to the virus when Molnupiravir was not present.

The circulation of specific mutations leading to decreased effectiveness of known therapeutics available for clinical use in Switzerland will be surveilled (see Section 6 below).

Impact on diagnostic tests
Nucleic acid detection may be affected by mutations in the RNA sequence of target regions. However, as RT-PCR tests use multiple targets, those mutations have not been reported yet to cause diagnostic failure.

Rapid antigen tests, theoretically may be affected by amino acid mutations in the N protein. However, diagnostic efficacy of antigenic tests appears to be relatively unaffected thus far, and various rapid diagnostic tests analytical sensitivity was conserved in detecting all variants, including Delta. (*Bekliz et al. MedRxiv. 2021*).

Considering potential transmissibility, immune escape, and diagnostic issues, the variants presented below will be particularly surveilled:

- variants classified as VOCs: B.1.351 (Beta), P.1 (Gamma), B.1.617.2 (Delta) – and their sub-lineages
- variants that include E484K + N501Y: higher transmissibility, immune escape risk, resistance to mAbs – until sufficient monitoring suggests they do not have a replicative/escape advantage) such as B.1.621 (Mu).
- variants that include L452R: increased transmissibility, resistance to mAbs, such as: B.1.617.2 (Delta) and C.37 (Lambda)
- Any Delta sub-lineage with a transmissibility advantage, immune escape properties or increased severity.

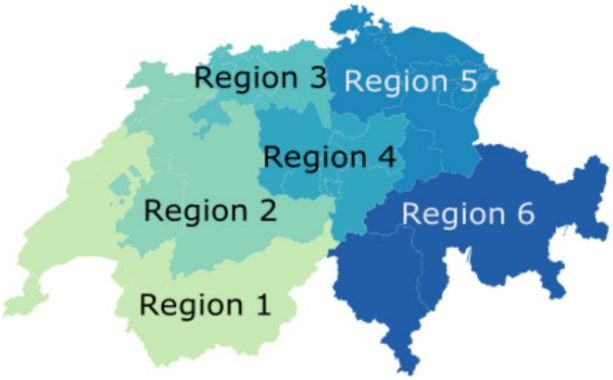
4. Epidemiology in Switzerland and number and origin of sequences produced through the program during the surveilled period

Data in this report comes from 3 sources: 1) The publicly available data on COVID-19 as reported by the FOPH (https://www.covid19.admin.ch), including data that is declared to the FOPH by the different laboratories in Switzerland; 2) data originating from laboratories participating in the surveillance program; and 3) sequences submitted to GISAID, for which the corresponding infected person was in Switzerland (resident or recent travel history to Switzerland).

General caveat: the numbers and denominators are fluid and variable over time; and are subject to change depending notably on the different databases used, and variable declaration delays. All data generated by this program is also submitted to SPSP.

The number and origin of sequences submitted to GISAID by each laboratory during January and February, 2021, prior to the start of the surveillance program can be found in the first report covering the months of March and April 2021.

Data will be presented here by regions, using the same region definitions that are used for the influenza sentinel surveillance system in Switzerland. Data are presented according to residency post-code.



Region 1 includes the cantons of Geneva, Neuchatel, Vaud and Wallis

Region 2 includes the cantons of Bern, Fribourg and Jura

Region 3 includes the cantons of Aargau, Basel (Basel-Stadt and Basel-Land) and Solothurn

Region 4 includes the cantons of Luzern, Unterwalden (Obwalden and Niedwalden), Schwitz, Uri and Zug

Region 5 includes the cantons of Appenzell (Appenzell Ausserrhoden and Appenzell Innerrhoden), Glarus, Sankt Gallen, Schaffhausen, Thurgau and Zurich.

Region 6 includes the cantons of Graubünden and Ticino.

Divisions of the different regions, from https://covariants.org/per-country

Submission delays have been reduced in the month of October, and the timeliness overall greatly improved.

Number of cases processed by the laboratories participating in the surveillance program

During the period covered by the present report, the FOPH reported a total of over 32 996 confirmed SARS-CoV-2 cases in Switzerland. Supplementary Table 1 provides an overview of the number and incidence of confirmed cases, the effective reproduction number R_e, the number and incidence of tests, test positivity, the number and proportion of sequenced samples, and the number and proportion of VOCs by canton, region and for Switzerland overall.

As of the writing of this report, the laboratories participating in this program reported 12,633 positive tests during the surveilled program, which represents about 38% of the total number of cases reported in Switzerland (including both PCR and antigen-based tests). Because of reporting delays, this number may be underestimated. Detailed data regarding the total number of tests performed each week by the laboratories participating in the surveillance program (including negative and positive tests numbers, and the number of the positive tests that have been sequenced) are available in appendix Table 3.

Number of declared SARS-CoV-2 sequences produced through the surveillance program (presented by submission date, further declarations are still ongoing)

A total number of 5,917 SARS-CoV-2 sequences have been declared to have been submitted to GISAID during this period. More than 7,000 sequences are available for this period on GISAID, and the difference may be explained by reporting delays.

This represents around 18% of all cases detected in Switzerland during the surveilled period (see Supplementary Table 2 and 3 in the Appendix for details). Of note, this number includes sequences from samples received from other laboratories in order to ensure sequencing of post-vaccination infections.

Table 2 shows the number of sequences successfully submitted to GISAID through the surveillance program during the surveilled period by calendar week (data is incomplete).

Week	Date	Number of sequences declared and successfully submitted to GISAID during the surveilled period, by all laboratories in the program
40	Oct 4 to Oct 10	1360
41	Oct 11 to Oct 17	1354
42	Oct 18 to Oct 24	1640
43	Oct 25 to Oct 31	1563
	Total	5917

Table 2: number of sequences submitted to GISAID through the surveillance program. Note these data are not by sampling date but rather by submission to GISAID date. Data are incomplete due to late reporting by one laboratory

The total number of SARS-CoV-2 sequences declared and submitted to GISAID by each laboratory during the month of October is available in Supplementary Table 3 in the appendix.

Covering of sequencing in Switzerland and contribution of the national SARS-CoV-2 surveillance sequencing program

As shown in Figure 1, the total number of SARS-CoV-2 sequences submitted per week generally increased towards the end of October (weeks 40 to 43), reflecting the increase in cases within Switzerland in the latter half of October. Almost all of the sequences available in GISAID (green curve) and those on which the surveillance is conducted, come from the national surveillance program.

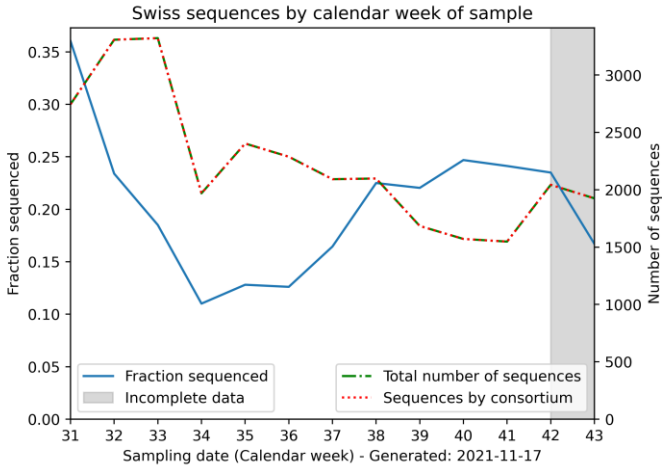


Figure 1: Number of SARS-CoV-2 sequences available for Switzerland (total available Swiss sequences in GISAID in green, Swiss sequences submitted through the program in dotted orange) and fraction of the total number of positive cases declared to the FOPH that have been sequenced (blue curve).

During the surveilled period, the total proportion of positive sequenced cases generally remained around 15-20%, above the aim of the program.

Figure 2 displays the number and fraction of SARS-CoV-2 cases sequenced for each Swiss region. Region 6 continued to have the lowest total number of sequences, while regions 4 and 5 continued to have the lowest fraction of cases sequenced, but were still well above the 10% goal.

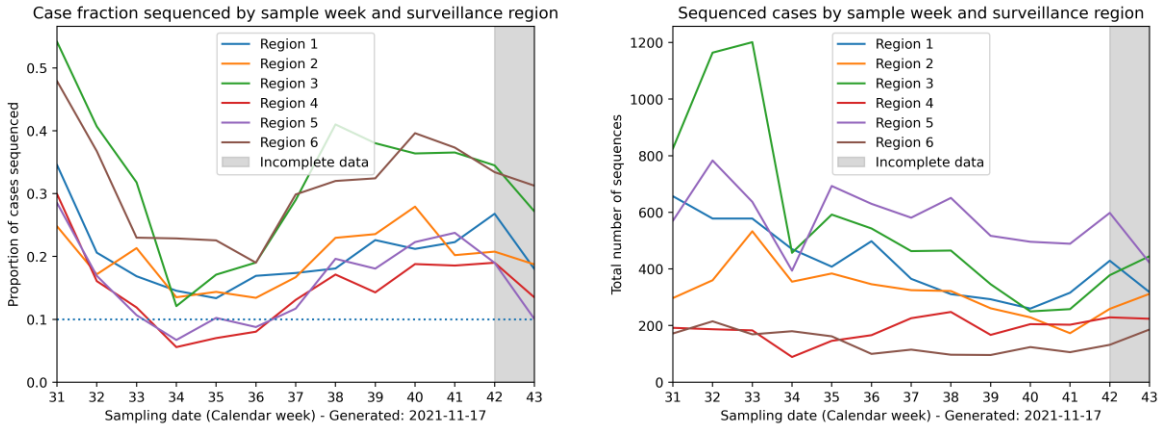


Figure 2: Sequencing coverage among the different Swiss regions per week, presented by fraction of cases sequenced (left) and by number of sequences (right).

5. Variants circulating in Switzerland since January 2021, with a focus on the surveilled period

Determination of the proportion of total number of sequences over time falling into defined variant groups is done by Emma Hodcroft's team and displayed on the CoVariant website (https://covariants.org/per-country). Those results are based on the total number of sequences submitted to GISAID over the time period for Switzerland. Those data mainly, but not exclusively, come from the national genomic surveillance program since its beginning (see Figure 1).

The B.1.617.2 Delta variant (in green in Figure 4) and its sub-lineages were almost exclusively retrieved during the month of October all over Switzerland, accounting for around 99.9% of the submitted sequences (see Figures 5 and 6). See Table 2 below for details. Neither Mu nor Lambda were retrieved at all in Switzerland during the surveilled period (table 3).

Region	Delta	Alpha	Beta	Gamma	B.1.1.318	Others	sequences	cases	% sequenced
All	7286	0	0	0	2	2	7290	32996	21.5
1	1381	0	0	0	0	1	1382	6012	22.0
2	1009	0	0	0	0	0	1009	4588	21.2
3	1363	0	0	0	2	0	1365	4127	32.3
4	865	0	0	0	0	0	865	5051	17.0
5	2078	0	0	0	0	0	2078	11631	17.2
6	548	0	0	0	0	1	549	1587	34.5

Table 3: number of sequences corresponding to selected variants in each region of Switzerland during the month of October 2021. No Alpha, Beta, Gamma, Lambda, Mu, etc. were identified, according to data received by November 17.

Many sequences are assigned to AY* lineages, which are Delta sub-lineages. AY.43 is the most common sub-lineage in Switzerland, and has remained stable at about 30%. A summary of the main new Spike mutations spotted across various Delta sub-lineages is available in section 3 of this report, describing the main VOC/VOIs.

Within Delta-sub-lineages, AY.4.2 remained rare during the month of October in Switzerland: among 7290 sequences retrieved during the surveilled period, 43 were AY 4.2. Despite this rarity, it has none the less increased in proportion, representing 0.6% of the cases at the end of October, compared to 0.3% at the end of September.

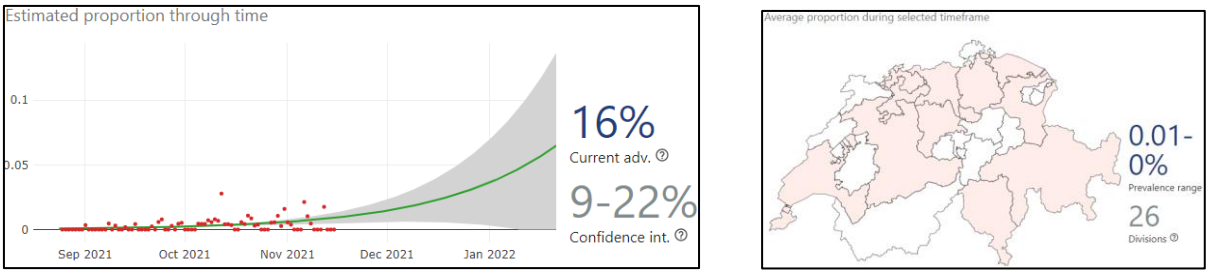


Figure 3: AY.4.2 estimated transmission advantage over time compared to co-circulating strains (left) and geographic distribution across Switzerland and average proportion during the surveilled period (right). Dynamic navigation available at https://cov-spectrum.ethz.ch/explore/Switzerland.

A new delta sub-lineage containing the E484Q and V687I mutations described above was detected in Geneva during the month of October. It has been closely followed and it appears to be declining in prevalence, apparently outcompeted by other Delta sub-lineages.

Among other sequences identified in Switzerland during the surveilled period, very few other lineages were recorded as of data received by November 25. Only 4 samples with identifiable non-Delta lineages were detected, notably: 1x B.1.640 sequence and 2x B.1.1.318 sequences.

An estimate of the total number of VOCs circulating in Switzerland, corrected by taking in account the fraction of sequencing in Switzerland is available through the covSPECTRUM program, developed at ETHZ, at https://cov-spectrum.ethz.ch/explore/Switzerland.

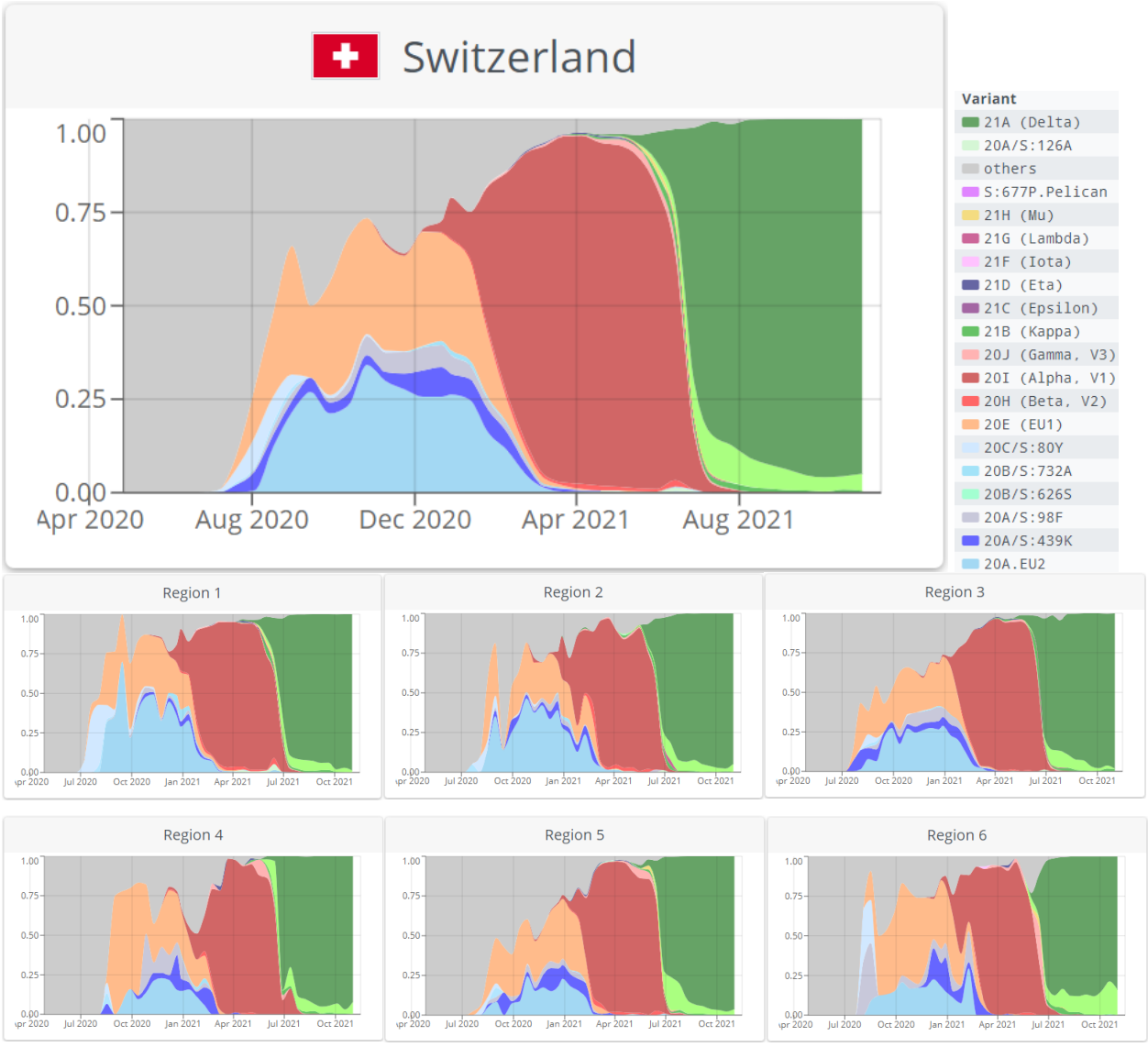


Figure 4: proportion of the total number of sequences (not cases), over time, that fall into defined variant groups, for Switzerland. Screenshot from CoVariant website. Dynamic navigation is available at https://covariants.org/per-country. Dark green indicates the currently dominant B.1.617.2 (Delta) lineage or its sub-lineages. Dark Red indicates B.1.1.7 (Alpha), the previously dominant lineage in Switzerland.

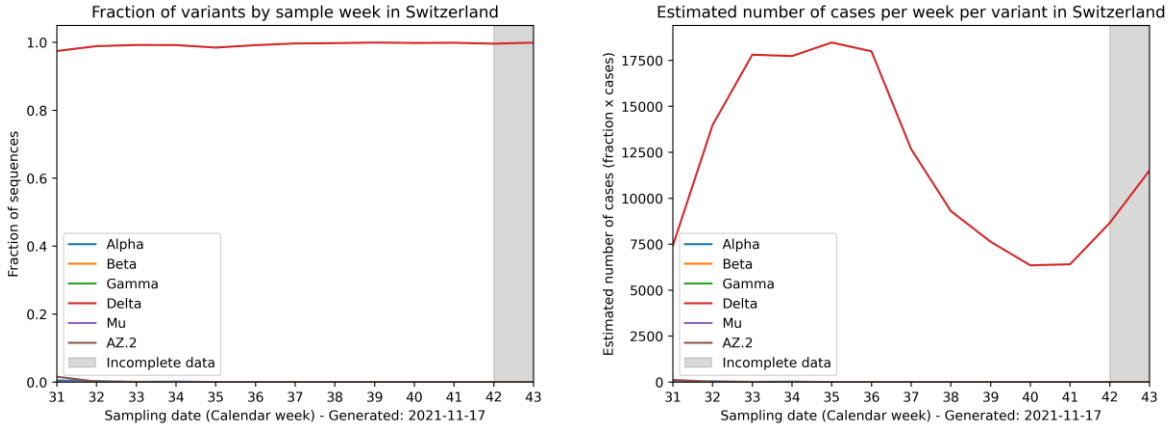


Figure 5: (Left): Percentage of circulating VOCs and VOIs in Switzerland by week, over the 43 first weeks of 2021 (total number of B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), B.1.617.2 (Delta) and B.1.621 (Mu) sequences from Switzerland and successfully submitted to GISAID are shown here).
(Right): Estimated number of sequences of the main VOCs/VOIs and variants under monitoring retrieved during the surveilled period.

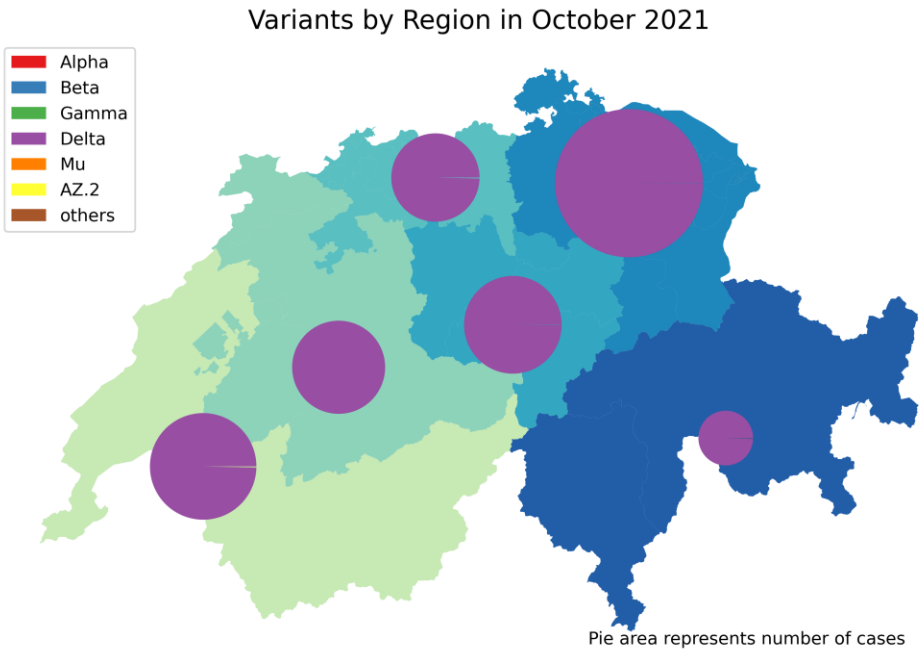


Figure 6: Distribution of variants per region, for October 2021, shown on a map. The size of the pie chart corresponds to the total number of sequences. Note the dominance of Delta or one of its sub-lineages in all regions.

6. Assessment of the competition between the different variants in Switzerland

The competition between different SARS-CoV-2 variants can be modelled using multinomial logistic regression. The analysis by Dr. Althaus' group is based on sequences retrieved from CovSPECTRUM. The results confirmed that Delta remains the only dominant SARS-CoV-2 variant in Switzerland in October 2021.

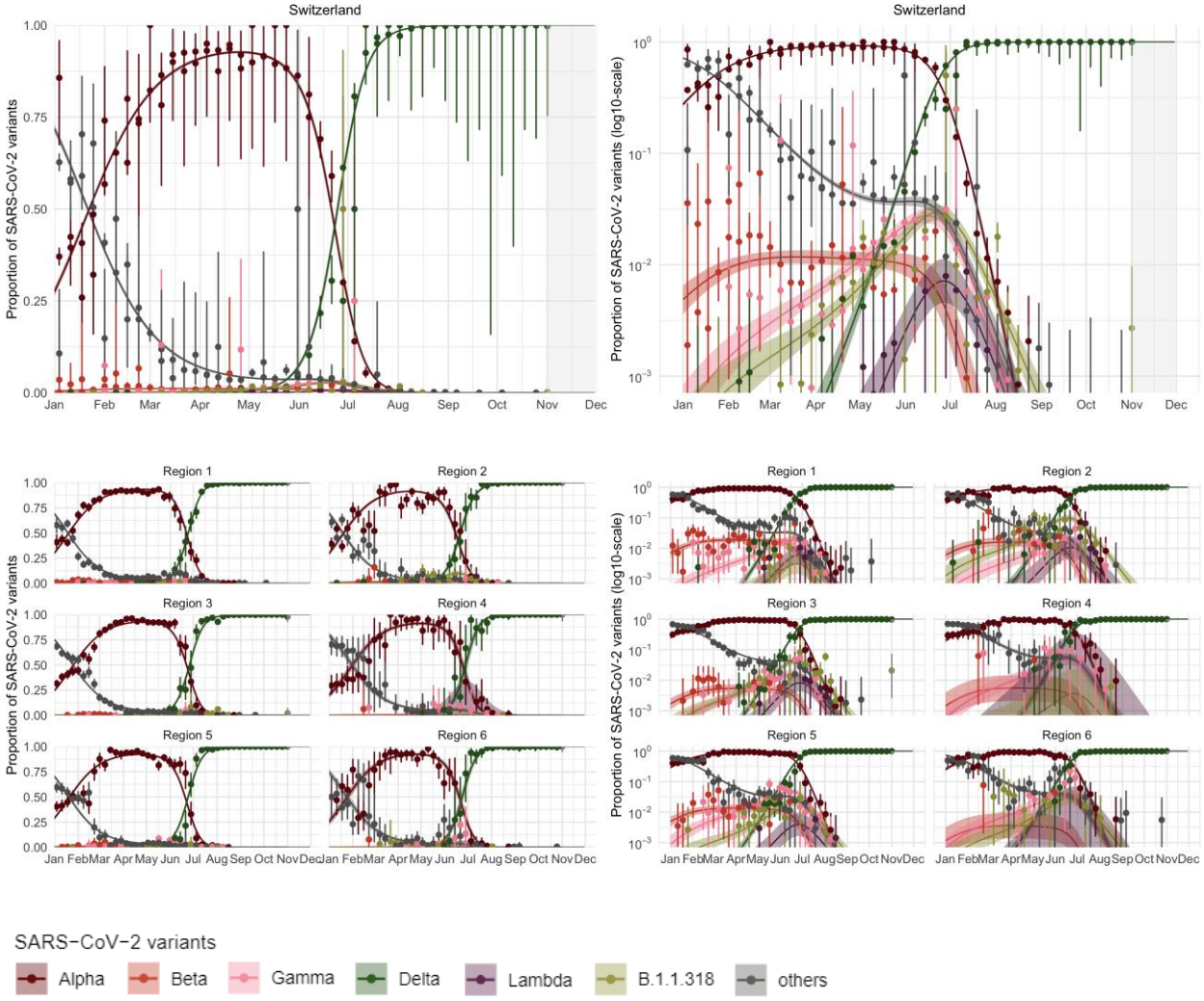


Figure 7: Observed and modeled proportion of SARS-CoV-2 variants over time in Switzerland. In April and May 2021, Gamma and Delta started to replace Alpha, with Delta now outcompeting all other variants. At the end of October, more than 99.9% of the retrieved sequences in Switzerland were due to Delta or one of its sub-lineages. No new variants appear to be displacing Delta. Model fits are based on a multinomial logistic regression with splines.

7. Surveillance of mutations associated with reduced mAb treatment efficacy

As a number of mutations have been reported to result in significantly reduced *in vitro* effectiveness of the sotrovimab and casirivimab/imdevimab association monoclonal antibodies used to treat patients in Switzerland, the prevalences of these mutations and similar mutations are being followed (Table 4).

	337H		337L		337R	337T	
date	Global	Switzerland	Global	Switzerland	Global	Global	Switzerland
2021-10-04	0	0	4	0	0	1	0
2021-10-11	1	0	5	0	0	3	0
2021-10-18	0	0	7	1	0	10	0
2021-10-25	0	0	5	0	0	3	0

	340A		340K		340G		356T
date	Global	Switzerland	Global	Switzerland	Global	Switzerland	Global
2021-10-04	2	0	8	0	0	0	0
2021-10-11	1	0	8	0	1	0	0
2021-10-18	6	0	14	0	1	0	0
2021-10-25	4	1	7	0	0	0	0

	K444T		V445A		D406D		G476D	
date	Global	Switzerland	Global	Switzerland	Global	Switzerland	Global	Switzerland
2021-10-04	1	0	18	0	2	0	3	0
2021-10-11	0	0	7	0	2	0	2	0
2021-10-18	1	0	12	0	3	0	0	0
2021-10-25	0	0	6	0	2	0	5	0

Table 4: Global and Swiss counts of sequences bearing escape mutations from therapeutic mAbs used in Switzerland

So far, no known mutations enabling complete escape from these therapeutic mAbs (sotrovimab and association of casirivimab/imdevimab) have been detected in Switzerland, and they remain rare globally.

8. Wastewater surveillance program

Since August, the B.1.617.2 (Delta) variant and its sub-lineages have accounted for the vast majority of the sequences identified in all of the six wastewater treatment plants (WWTPs) that are tested on a daily basis. Detection of variants in wastewater can be challenging if the prevalence is low due to low RNA concentrations, as was the case in June and July, and again lately in October (https://sensors-eawag.ch/sars/overview.html). In this situation, it is especially difficult to distinguish related lineages that share variant-defining mutations. In particular, this is the case, among the sub-clades of B.1.617*, and especially amount the AY.* sub-lineages of B.1.617.2.

During the month of October, the dominance of B.1.617.2 (Delta) was obvious in all surveyed WWTPs.

The AY.4.2 sub-variant being defined by only two mutations on the S gene, both of which are individually present at some frequency in other sub-lineages, confidently identifying it in wastewater samples is more technically challenging. As both mutations occur close enough on the SARS-CoV-2 genome sequence, it is sometimes possible to detect them both co-occurring on the same RNA fragment, which provides strong evidence of the presence of the variant. This method of detection identified the AY.4.2 sub-variant in the October 3 sample from the Geneva WWTP (Vernier/Aire), where 120 out of 121 RNA fragments of the corresponding genomic region showed co-occurrence of the two AY.4.2 defining mutations, indicating its presence during the month of October. This observation was repeated in the same WWTP on October 10, but with only 2/2 fragments bearing the defining mutations.

This is in line with the detection of AY.4.2 samples in respiratory specimens collected for diagnosis purpose and sequenced through the SARS-CoV-2 genomic and variants surveillance program since the beginning of October in the canton of Geneva.

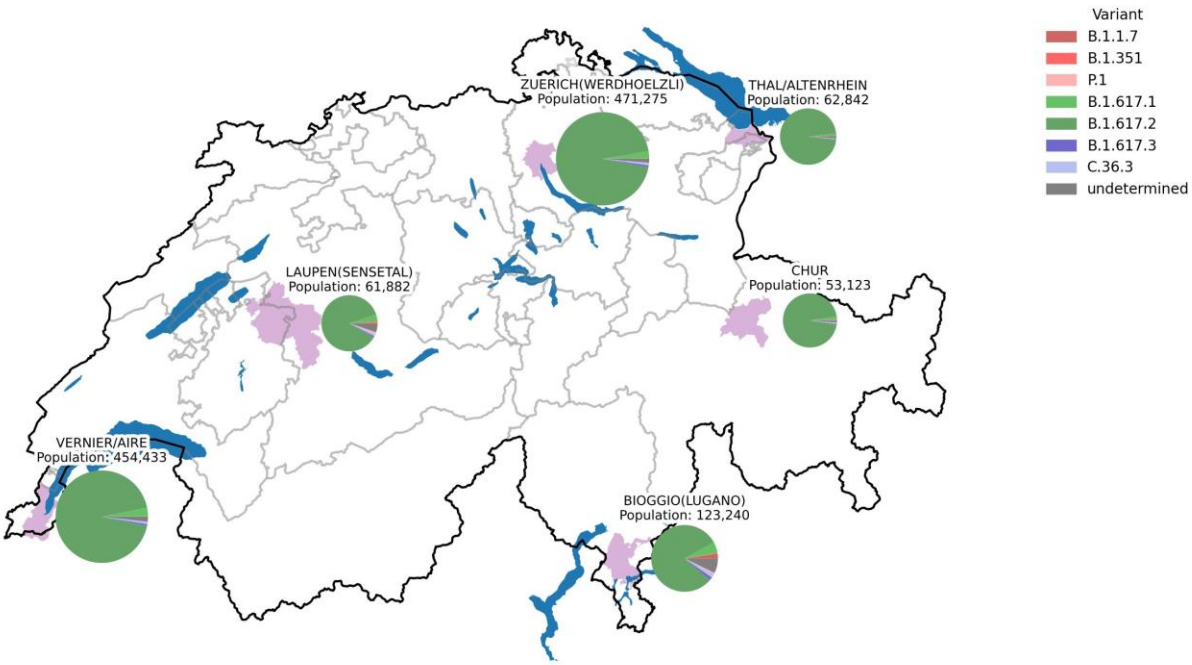


Figure 8: Overview of the average prevalence of variants of SARS-CoV-2 estimated from wastewater samples collected daily during the month of October in WWTPs located in 6 different Swiss locations. Pie chart areas are proportional to population connected to the wastewater treatment plants. Pink shaded areas represent catchment areas (boundaries from 2017). Population connected to Vernier (GE) wastewater treatment plant also includes ~44,000 inhabitants from neighboring French communities. B.1.617.2

(Delta) is represented in in dark green, B.1.617.1 in light green (Kappa), B.1.617.3 in purple, B.1.1.7 (Alpha) in dark red, B.1.351 (Beta) in light red, P.1 (Gamma) in pink.

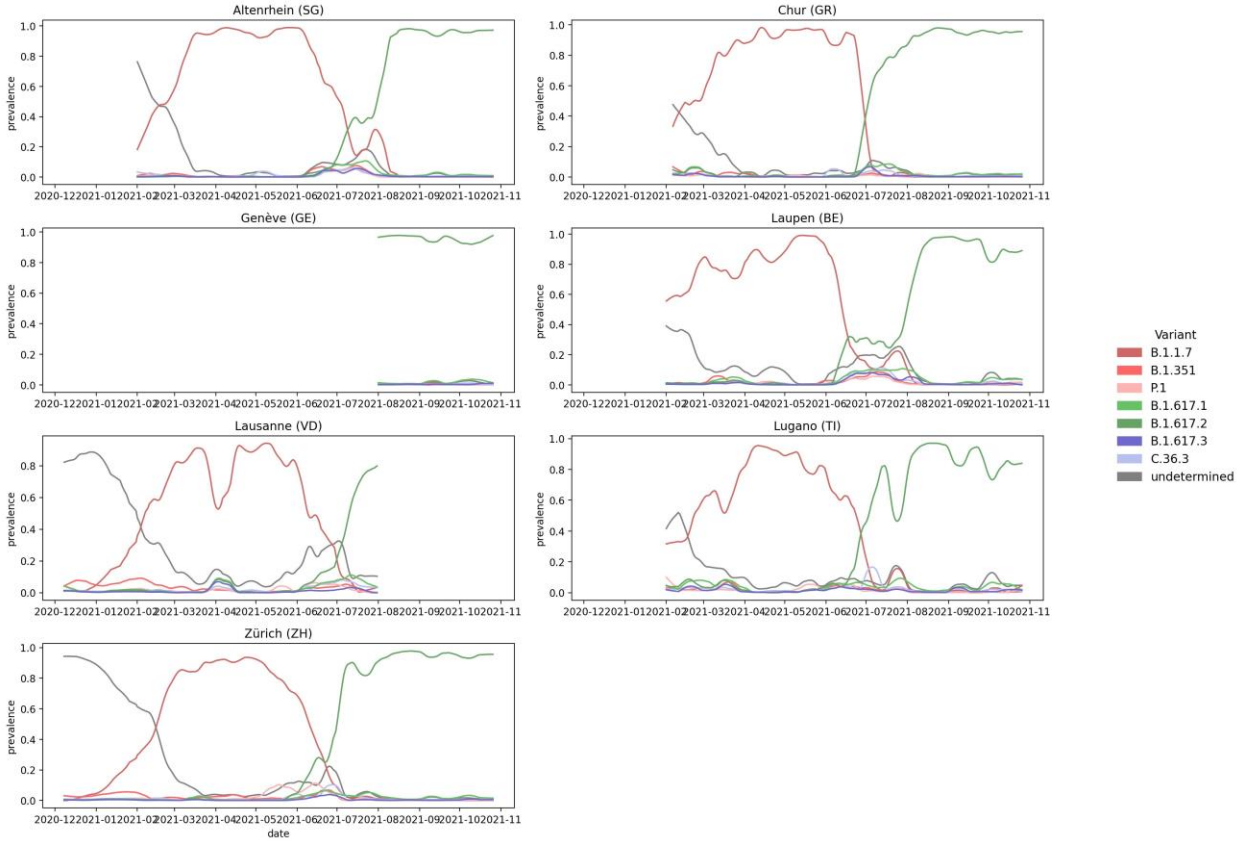


Figure 9: Prevalence of variants of SARS-CoV-2 estimated from wastewater samples collected daily until October 31 (except Lausanne: July 31) in WWTPs located in 7 different Swiss cantons. B.1.617.2 (Delta) is represented in dark green, B.1.617.1 (Kappa), in light green, B.1.617.3 in purple, B.1.1.7 (Alpha) in dark red, B.1.351 (Beta) in light red, P.1 (Gamma) in pink. Online dynamic navigation available at https://bsse.ethz.ch/cbg/research/computational-virology/sarscov2-variants-wastewater-surveillance.html.

9. Immunological characterization of the variants

During the month of September and October, neutralization titers of sera from 48 vaccinated individuals, 48 convalescent individuals and 55 individuals who were previously infected and then vaccinated (n=151 total) were assessed using Spike proteins harboring the full set of mutations found in 10 different lineages and each of the mutations (T19R/delta156-157/R158G/L452R/T478K/D614G/P681R/D950N) found in the delta B.1.617.2 variant using purified spike protein trimers in the high-throughput surrogate spike-ACE2 (S^3-ACE2) neutralization assay.

Comparison of neutralizing antibody (nAb) titers for vaccinated versus infected people:

As shown in Figure 10, a comparison of the neutralization titers of serum from people who received 1 dose (n=21) versus 2 doses (n=27) of Moderna (n=13) or Pfizer-BioNTech (n=35) vaccines reveals that the Beta and Delta strains are poorly neutralized after a single dose of vaccine. The decreased neutralization of the Delta variant can be attributed mainly to the L452R mutation. The combination of the two mutations E484Q + L452R (present in the Kappa variant and in a Delta sub-lineage found in Geneva isolates from the past weeks) is poorly neutralized. None of the other Delta mutations significantly affect neutralization. Neutralization titers are greatly improved by a second dose of vaccine for all tested Spikes variations, including the Delta, E484Q or E484Q+ L452R mutated Spikes.

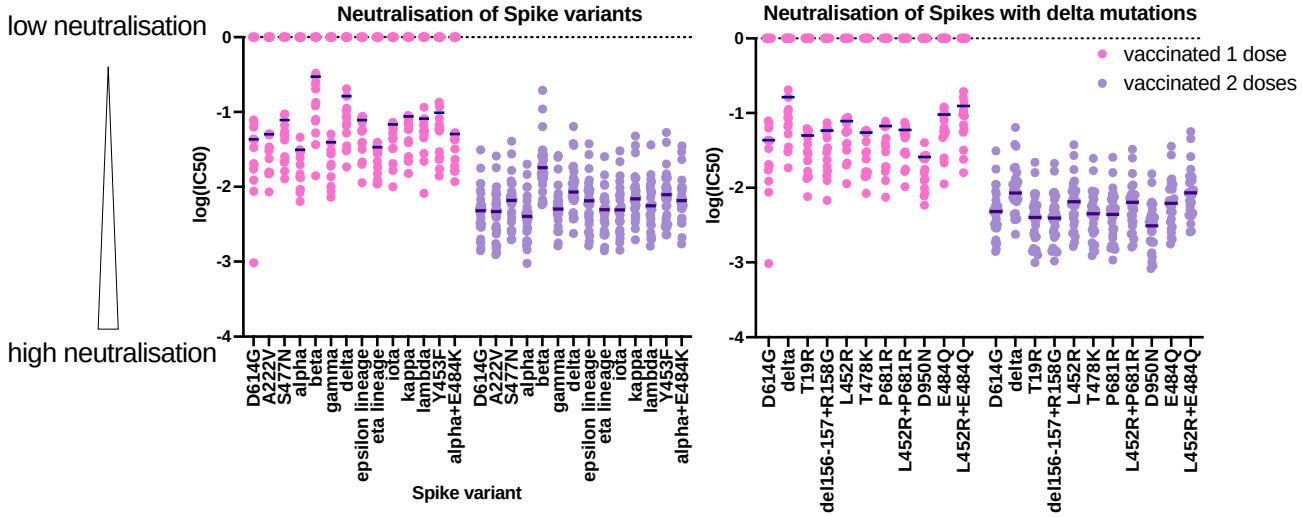


Figure 10: The S^3-ACE2 Luminex-based neutralization assay was used to determine the serum dilution giving 50% inhibition in neutralization (IC50). A higher IC50 dose corresponds to a lower serum dilution necessary to achieve the 50% inhibition of neutralization. Sera from people vaccinated either with only 1 dose (without previous known infection) or with 2 doses were compared. Spike variants from past or actual VOIs or VOCs or mutations found in B.1.617.2 were included in the assay. The Y453F was added as it was recurrently found in Mink-farm associated clusters.

Using a subset of sera collected within the same time frame after infection or vaccination (16 to 95 days) higher neutralization titers were measured for vaccinated compared to infected individuals, notably against the Gamma and the (currently circulating) Delta Spikes (Figure 11 A,B), even though infected people were on average younger than vaccinated people in the studied group (Figure 11 C). A third group of people who were first infected and then received 1 dose of vaccine displayed on average higher titers of nAbs against all tested Spikes compared to “vaccinated only” people, although the earlier sampling of only vaccinated versus infected + vaccinated individuals (24.2 days versus 41.5 days, Figure 11 B,D) may be a confounding variable.

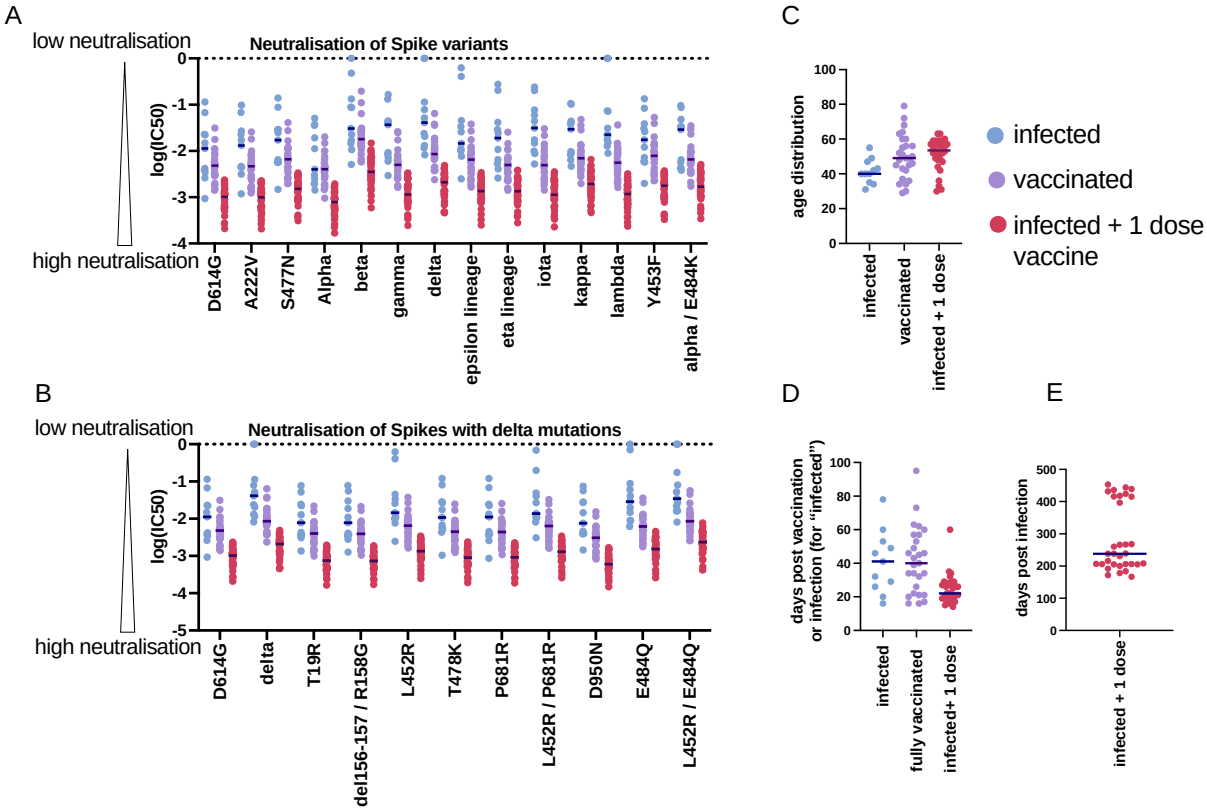


*Figure 11: **A-B**: The S[3]-ACE2 Luminex-based neutralization assay was used to compare neutralization of the indicated Spike variants or mutations by sera from people either infected (n=11), fully vaccinated (n=27), or infected then vaccinated with a single dose of vaccine (n=32). Of note, infected individuals were all infected before March 2021, before the expansion of the Delta lineage. **C**: Distribution by age of the different groups. **D**: Time after infection, full vaccination or single vaccination for the different groups. **E**: Time after infection for the group of people both infected and vaccinated with 1 dose of vaccine.*

Focusing on nAb titers against the Delta variant reveals a more robust response in vaccinated compared to infected people up to 95 days post vaccination (Figure 12).

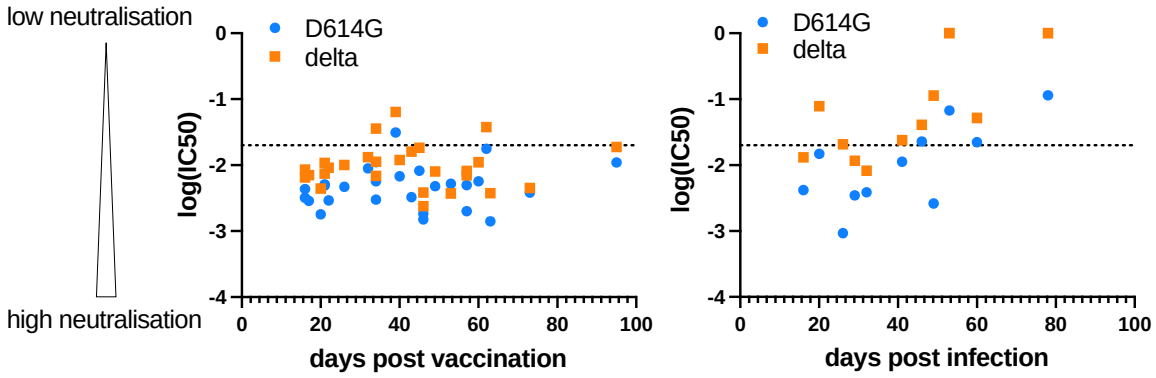


Figure 12: IC50 values representing nAb titers for sera obtained within 16 to 95 days after full vaccination or infection.

nAb titers after Moderna versus Pfizer-BioNTech vaccines

Comparing sera from individuals fully vaccinated either with Moderna (n=8) or Pfizer-BioNTech (n=19) vaccines reveals comparable nAb titers against the tested Spike proteins, even though sampling was performed at later time points after Moderna than Pfizer vaccination (56 days versus 35.4 days) (Figure 13).

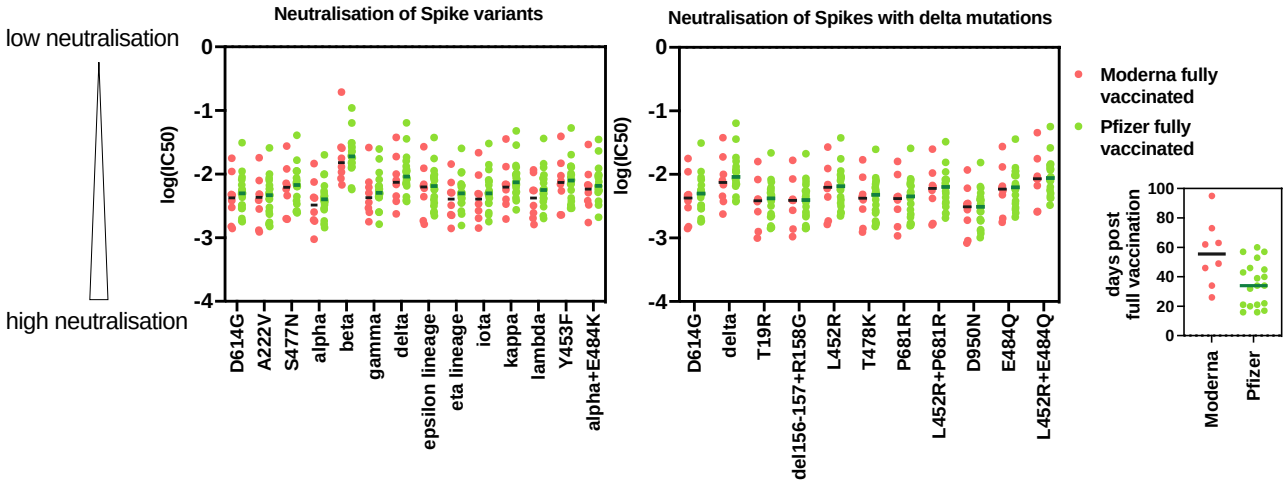


Figure 13: The S[3]-ACE2 Luminex-based neutralization assay was used to compare neutralization of the indicated Spike variants or mutations by sera from people vaccinated with 2 doses of either Moderna or Pfizer-BioNTech vaccines.

Comparison between anti-S binding antibodies (Abs) and nAb titers

A comparison was performed between anti-S binding antibody titers, as measured with currently used serological tests (Roche Elecsys anti-S), and neutralizing antibody titers against the D614G ancestral variant or the currently circulating Delta variant (Figure 14). No clear correlation could be observed between the 2 serological assays for either Spike protein, demonstrating the limitation of currently used serological assays to predict the neutralization potential of serums.

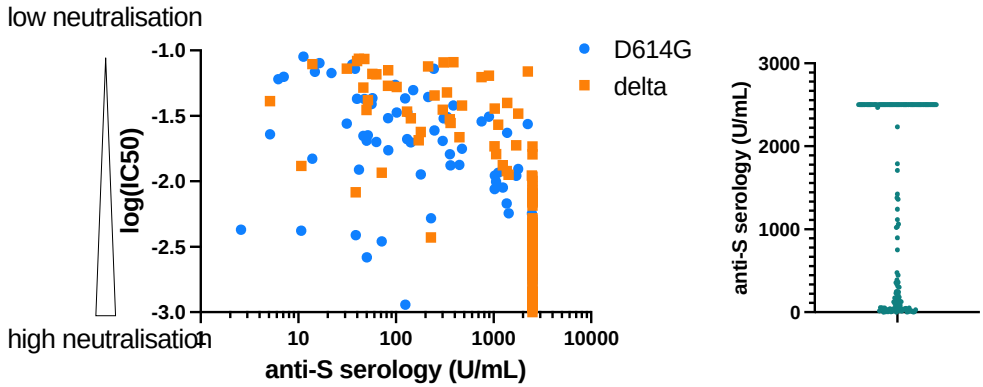


Figure 14: left panel: nAbs titers for sera from infected, vaccinated or infected then vaccinated people (n=151) are compared to anti-S Abs titers as obtained with standard Roche Elecsys anti-S procedure. Right panel: distribution of the anti-S Elecsys titers.

Heterogeneity in nAbs titers for Spike variants in the population

We separated the sera (n=151) in 3 classes depending on the anti-S serological titers determined by the standard procedure (Roche Elecsys anti-S): positive but low (anti-S titer<50 U/mL), medium (>50 U/mL, <2000 U/mL) and high (>2000 U/mL). Neutralization of Spike variants with high anti-S titers sera is homogeneous in the population tested, with loss of efficiency only in the case of the Beta Spike (Figure 15). However, results are markedly heterogeneous for sera with low or even medium anti-S titer, whether for neutralization of Beta, Eta, Lambda, Alpha+E484K or the currently predominant Delta Spike proteins.

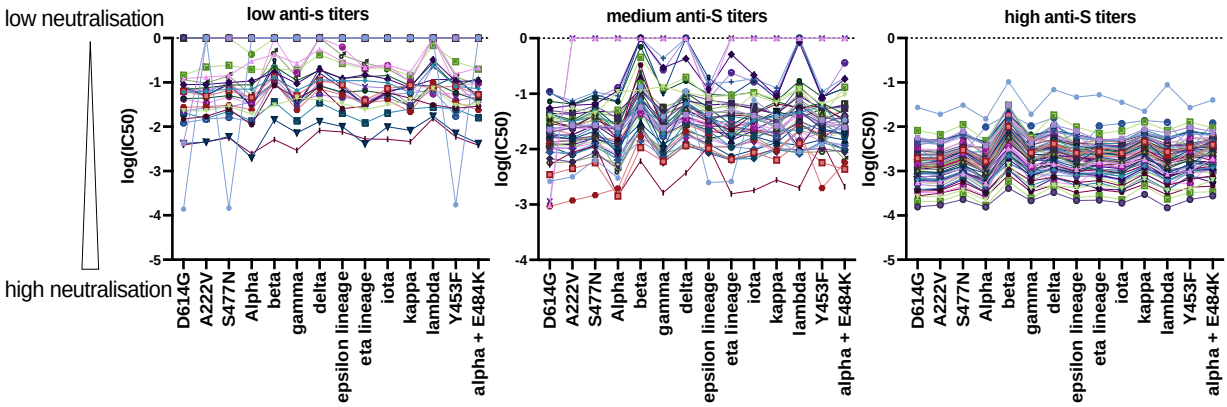


Figure 15: Sera from infected, vaccinated, infected then vaccinated people were classified in 3 groups depending on their anti-S serological status: low (n=30), medium (n=46) or high (n=75) anti-S. The log value of the serum dilution necessary to achieve 50% inhibition of neutralization for each individual and for each Spike variant is plotted.

Conclusion

In October, over 7,000 sequences were obtained for Switzerland, through this surveillance program, in the midst of an increase in case numbers in the latter half of the month. Each week since this surveillance program started, it has contributed almost all of the Swiss SARS-CoV-2 sequences available on GISAID.

In October, around 18% of the cases reported in Switzerland were sequenced, similar to the month before. This reflects that case numbers are currently low compared to sequencing capacity. Region 4 and 5 are still the least represented geographical areas, but the goal of 10% coverage has been met.

It continues to be nearly exclusively the B.1.617.2 (Delta) variant (and its sub lineages) that circulates, with a relatively homogenous representation over the different Swiss regions, accounting for around 99.9% of the sequences identified in October.

Numerous sub-lineages are increasingly detected, but no sub-lineage is experiencing rapid growth.

Delta sub-variants with Q or A mutations at spike position 484 are being increasingly identified in independent clusters. While position 484 has been linked to reductions in neutralization, multiple lines of evidence suggest that 484Q mutations in Delta are not particularly concerning. While multiple unrelated clusters of viruses with 484 mutations have been identified, none show any signs of a growth advantage at this time. Despite this, the trend of increasing detection of mutations at this site deserves further monitoring.

All other variants were only rarely detected, both in clinical samples and in the wastewater surveillance part of the program.

One non-Delta sequence was identified by the sequencing program belonging to a newly designated variant B.1.640. This new variant is apparently extremely rare, both in Switzerland and worldwide, but the large number of mutations and the possession of mutations at certain signs are cause for closer scrutiny.

No important geographical breakdown of a particular variant has been noticed.

No additional diagnostic or treatment issues were noted for any variant in October.

Immunological data confirmed the escape properties of some mutations, the higher nAb titers after vaccination than natural infection, and the heterogeneity of the nAb titers in the general population after infection. Note that immune characterization of the specific Delta sub-lineage containing the E484Q retrieved in Geneva is ongoing.

An estimate of the total number of VOCs circulating in Switzerland, corrected by taking in account the fraction of sequencing in Switzerland is available at https://cov-spectrum.ethz.ch/explore/Switzerland.

As this report was being finalized, a new variant of concern Omicron (B.1.1.529) with the most spike mutations ever seen was detected, with an apparent origin in southern Africa. Although this was spotted in November, outside the period covered by this report, it deserves mention. No case of transmission within Switzerland is known at the time of this report, but a probable case from a traveler coming from South Africa has been reported.

Acknowledgements:

https://bsse.ethz.ch/cevo/research/sars-cov-2/swiss-sars-cov-2-sequencing-consortium.html

Prof. Silvia Stringhini, Prof. Idris Guessous and Zaballa Maria Eugenia for the immunological characterization of the variant Spike proteins.

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Appendix:

SARS-CoV-2 epidemiology in Switzerland:

We used publicly available data on COVID-19 as reported by FOPH (https://www.covid19.admin.ch) and sequence data submitted to GISAID to provide a summary of the SARS-CoV-2 epidemiology in Switzerland. Data presented here cover the period from October 4 to October 31.

sup_table_overview_Oct.xlsx

Supplementary Table 1: Epidemiological data for Switzerland, its regions and cantons in October 2021: population, number and incidence of confirmed cases, effective reproduction number R_e, number and incidence of tests, test positivity, number and proportion of sequenced samples, and number and proportion of VOCs. R_e by region is represented as the median and range of the daily R_e values for all cantons within a region.

week	date	Total PCR tests	Positive tests	Sequenced	% positives	% positives sequenced
40	Oct 4 to Oct 10	49568	2 411	1 360	4.86%	56.41%
41	Oct 11 to Oct 17	49994	2 354	1 354	4.71%	57.52%
42	Oct 18 to Oct 24	62300	3 486	1 640	5.60%	47.05%
43	Oct 25 to Oct 31	70904	4 382	1 563	6.18%	35.67%
	Total	232766	12 633	5 917	5.43%	46.84%

Supplementary Table 2: Total number of tests performed by the laboratories participating in the surveillance program from October 4 to October 31, 2021.

		Basic Surveillance						Augmented Surveillance						Sentinella Laboratories		
Week	Date	EOC	St-Gallen	Labor Team W *	Risch	SRO	Synlab	USB	IFIK	Diana labs	CHUV	UZH	ICH-VS*	HUG	ETH/ Viollier	All
40	Oct 4 to Oct 10	43	48	186	23	12	19	55	55	44	30	112	62	74	587	1350
41	Oct 11 to Oct 17	31	48	186	20	18	23	58	66	44	25	192	40	77	484	1312
42	Oct 18 to Oct 24	51	48	186	0	22	19	62	54	94	37	200	73	126	669	1641
43	Oct 25 to Oct 31	58	48	186	27	22	28	85	33	2	36	42	44	103	762	1476
	Total	183	192	744	70	74	89	260	208	184	128	546	219	380	2502	5779

*Supplementary Table 3: number of sequences submitted to GISAID by each laboratory during the surveilled period (October 4 to October 31, 2021). *including sequencing sent to high-throughput platforms. ND = No data*

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