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

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1. Summary

In July, COVID-19 cases numbers declined in Switzerland, with vast majority of cases caused by BA.5.

Although case numbers were declining, circulation was relatively high at the start of July, lowering the fraction of sequenced cases. Approximately 1.2% of the total number of cases identified in Switzerland in July were sequenced by the Surveillance program, yielding over 2,000 sequences.

The vast majority of the sequences in Switzerland belong to BA.5, followed by BA.4. BA.4 is being clearly outcompeted by BA.5, even though they are identical in their Spike protein. Their spike protein closely resembles that of BA.2, with a few additional mutations, including a mutation at position 452 of its spike protein's binding domain.

The currently circulating BA.4/5 variants are resistant to all the antibody therapies used in Switzerland. In particular Evusheld®, which is composed of tixagevimab (complete resistance) and cilgavimab (partial resistance), and sotrovimab do not appear to have any clinical effectiveness. As far as preventing infection, these variants substantially escape immunity from vaccination and previous infections, although previous BA.1 and BA.2 do infections confer better protection. Protection against severe disease is conserved much better. Any differences in intrinsic severity of these variants appears to be masked by the protection afforded by vaccination or previous exposure. Most importantly the BA.4/5 wave has not resulted in a large increase of hospitalizations in Switzerland.

The circulation of BA.1 and Delta was extremely low in July, with only 1 sequence detected for each, thus their circulation has effectively stopped in Switzerland—the remaining sequences likely originate from chronic infections, not new cases. BA.2 circulation is currently very low in Switzerland, with 49 sequences detected in July.

Numerous highly derived BA.2 sublineages have appeared in India, most prominently the BA.2.75 sub-variant. Notably, 1 case of the BA.2.75 sublineage was detected (after having previously been detected in June's waste water). Preliminary data from India suggest a competitive advantage of BA.2.75 over BA.4/5 in some contexts. However, it is still unclear if it will outcompete BA.5. Numerous BA.4 and BA.5 sublineages, notably BA.4.6, are also displaying advantages over "basic" BA.4/5, and an increase in lineages carrying the R346T mutation in particular has been noticed within Switzerland.

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, 12 diagnostic laboratories are participating in the program, including university hospital centres in Switzerland (Geneva, Lausanne, Bern, Basel, Zurich, Ticino), in addition to private laboratories (Viollier; Medisupport including Dianalabs, Polyanalytic, Dianalabs Valais, Proxilab and Bioanalytica; Labor Team W, Risch), cantonal-based laboratories (Hôpital du Valais – Institut Central), Spital Region Oberaargau (Bern, Solothurn, Aargau, Luzern), and 2 high-throughput sequencing platforms (Health 2030 Genome Centre in Geneva, 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. 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>).

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

This report has been produced by Erik Boehm, Pauline Vetter, Marc Friedli, Samuel Cordey, Richard Neher, Christian Althaus, Martina Reichmuth, Cornelius Römer, Niko Beerenwinkel, David Dreifuss, Chaoran Chen, Tanja Stadler, Priscilla Turelli, Didier Trono, Emma Hodcroft, Silvan Heeb, Anna Fesser, 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 July 4 to July 31, 2022 (weeks 27, 28, 29, 30). 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

Five variants and their sub-lineages are considered VOCs by the WHO, B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), B.1.617.2 (Delta), and B.1.1.529 (Omicron). Worldwide, all VOCs except Omicron have essentially disappeared from samples collected within the last 30 days (<https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---20-july-2022>).

Omicron

The Omicron VOC (B.1.1.529) was first identified in southern Africa during November 2021 with an unprecedented number of mutations (>50 genomic, >30 on in the spike protein), most of which are associated with both immune escape and/or increased transmissibility. Currently, it has 5 sublineages: BA.1-5, many of which now have further “sub-sublineages”. Despite all being considered “Omicron”, some BA.X sublineages differ from each other (in terms of mutation counts) more than the earlier VOCs differed from the original Wu-1 strain.

These sublineages have successively replaced each other, first BA.2 replaced BA.1 (which had replaced Delta), and it is now being replaced by BA.4 and BA.5. Notably, BA.4 and BA.5 have identical spike proteins (differing in mutations outside of Spike), that differ significantly from BA.1 but differ from BA.2’s spike protein by only a few mutations. Both BA.4 and BA.5 contain the L452R mutation in their receptor binding domain (RBD), which is also found in Delta, and has been associated with both increased ACEII receptor affinity and decreased neutralization by monoclonal antibodies (mAbs) and poly-clonal sera.

Numerous highly derived BA.2 sublineages are also appearing, in particular, BA.2.75 has been growing rapidly in India where BA.4/5 circulation has remained low. The growth advantage outside of India appears much smaller and varies significantly by region. Preliminary results from Sweden, a population with an immunological history more similar to Switzerland, found no immune-evasion advantage of BA.2.75 compared to BA.5.

Subvariants of BA.4 and BA.5 containing additional mutations, particularly at position 346 of the spike protein (such as BF.7), are also cause for concern. In particular, BA.4.6 with the R346T mutation has signs of growth in many western countries.

Detection

All sub-lineages are still detected by RT-PCR tests, but BA.1,3,4, and 5 (but not BA.2) exhibit S-gene target failure with some assays that can be used as a proxy prior to sequencing, as seen with VOC Alpha (and due to the same deletion as found in Alpha). Due to the dominance of Omicron within Switzerland, the absence of S-gene target failure is currently a good proxy for BA.2 infection. Likewise, its presence is indicative of a likely BA-4/5 infection (rather than a BA.2 infection). All Omicron variants contain deletions in the N-gene that results in N-gene dropout when using the PCR test from Huwel Life Sciences, Hyderabad, India. Antigenic tests are still able to detect these variants.

All Omicron variants are still detected by rapid diagnostic tests, although a recent study suggested that the tests were significantly less sensitive to Omicron BA.2, the drop in sensitivity relative to the currently circulating BA.5 was minor. There is some evidence that sensitivity may decrease depending on the patient’s immune status, which may confound results.

Immune escape

Extensive data demonstrates that Omicron variants are substantially able to evade neutralizing antibodies (nAbs) from non-Omicron infections and after 2-3 doses of vaccine.

BA.4/5’s spike protein most closely resembles BA.2’s spike, differing by only 2 missense and 2 deletion mutations, most notably this includes L452R (found in Delta). BA.2.75 has 8 Spike mutations relative to BA.2. A recent study suggests that BA.2.75 escapes immunity raised against Delta infections better than any other variant. Data suggests low neutralization of BA.2.75 and BA.4/5 by sera from BA.1 and BA.2

vaccine-breakthrough infections. While all Omicron sublineages largely escape humoral immunity, cell mediated immunity remains mostly intact.

A recent publication found that BA.4 or BA.5 convalescent sera poorly neutralizes (a 2.4 to 2-6 fold reduction) the BA.4.6, 4.7, and 5.9 sublineages – all of which contain either R346T or R346S mutations. Furthermore these sublineages completely escape neutralization by Evusheld and have substantially reduced neutralization by sotrovimab.

A 3rd vaccine dose or a combination of previous infection and 2 vaccine doses results in poor neutralizing titers against the circulating BA.4 and 5, and a corresponding poor efficacy at preventing infection. Efficacy preventing hospitalization and death is reduced but remains high. Four doses improved efficacy at preventing symptomatic disease is relatively high (>60%), but remains poor (~30%) at preventing any infection.

Updated bivalent vaccines using the Omicron BA.1 sequence performed much better against the currently circulating BA.4/5 sublineages, but neutralization was still reduced by approximately 3-fold relative to BA.1. Given the continued divergence of SARS-CoV-2 (in particular the aforementioned BA.2.75, BA.4.6/7 and BA.5.9 sublineages), it is clear that additional updates would be very beneficial.

Escape from monoclonal antibodies is extensive too, and is covered by the “Therapeutic intervention effectiveness” section.

Severity

A multitude of clinical, *in vitro* and *in vivo* studies indicate that Omicron BA.1 and BA.2 cause intrinsically milder disease. Importantly, BA.1,2, and 3 use a TMPRSS2-independent entry pathway, and exhibit less cleavage of the spike protein and corresponding cell to cell fusion. This suggests an altered tropism that may favor replicating in the upper rather than lower respiratory tract, and is a possible explanation for observations of the infections being less severe.

Severity determinations are complicated by an over representation of reinfections/vaccine breakthroughs, which are expected to be mild due to the protective effect of prior vaccination/exposure. To date, no study has properly controlled for pre-existing immunity through serology studies (indeed, finding naïve individuals for inclusion into a test is becoming impractical).

BA.4 and BA.5 have apparently regained the ability to use TMPRSS2 mediated entry pathways and exhibit heightened cell to cell fusion relative to BA.1&2 (although it is still not quite as high as that of earlier variants), suggesting that their intrinsic severity may be closer to that of previous variants. Recently, a study in hamsters suggested that BA.4/5 is significantly more severe than BA.2, but the applicability of these results to humans is unclear (as similar results for BA.2 vs BA.1 failed to correlate with an obvious effect in humans). Significant protection is afforded by vaccination and past exposure, which may mask differences in intrinsic immunity, and render such differences largely irrelevant from a public health perspective.

The Delta VOC

Delta has become extremely rare in Switzerland, with only 1 case detected in July.

Therapeutic intervention effectiveness

All sublineages display complete escape from combination of casirivimab/imdevimab. A matched cohort study found very little clinical benefit of sotrovimab treatment during a BA.1 wave. Both *in vitro* and *in vivo* data suggests that sotrovimab is even less effective against BA.2,4 and 5. Indeed a study in Qatar failed to find any beneficial effect of sotrovimab treatment in the context of BA.2 infections. Currently, there is conflicting data regarding the efficacy of sotrovimab against BA.2.75: two studies report BA.2.75 is significantly more susceptible to sotrovimab than the parent BA.2 strain, while another reports that its sensitivity is unchanged. Further studies are needed to clarify.

Similarly, *in vitro* data suggests that both antibody components of Evusheld® (tixagevimab and cilgavimab) will have significantly reduced neutralization against BA.4/5, but one component (cilgavimab) should retain efficacy against BA.2. Interestingly, while BA.2.75 contains an escape mutation against cilgavimab

associated with up to a 12 fold reduction in neutralization, it also contains a reversion mutation that again renders it susceptible to tixagevimab. The overall effect is only a modest reduction in neutralizing activity against BA.2.75 relative to BA.2, and a substantial improvement relative to BA.4/5. From the perspective of patient treatment with mAbs, replacement of BA.4/5 with BA.2.75 would not be expected to be harmful.

As sotrovimab and tixagevimab/cilgavimab are being used, additional mutations causing escape from them will thus be closely followed (Table 1, and section 7).

In addition to mAbs, there are a number of other antiviral treatments under development, such as 3CL like protease inhibitors like Paxlovid® (PF-07321332, nirmatrelvir/ritonavir) or RNA nucleotide analogues (which interfere with replication of the viral genome, such as molnupiravir). Patients taking this drug have been noted to have a higher “rebound” frequency than those who do not take the drug. Importantly, while viral loads may go up when the drug is discontinued, the drug still efficiently limits viral replication when given. Resistance mutations to Paxlovid® have been noted, in particular L50F and E166Q. Notably, E166V has been observed to occur at higher frequencies in Paxlovid® treated groups during clinical trials. Given the low proportion of the population that receives Paxlovid®, it is unclear if there is enough selection pressure for these mutations to become common. Indeed, known escape mutations against Paxlovid® are currently very rare.

Resistance to molnupiravir comes at the cost of significantly reduced viral fitness, so limited use is unlikely to lead to resistant strains. Preliminary data confirms that molnupiravir, Paxlovid®, and remdesivir all retain full *in vitro* efficacy against Omicron sub-lineages.

AA position	World	Europe	Switzerland	Mutations
Sotrovimab				
337	9	4	2	R/L/H/T
340	52	36	2	K/A/G/Q/V
356	86	33	0	T
377	0	0	0	K
Cilgavimab				
346	13 679	4 745	59	I/K/S/T
444	566	171	1	E/Q/R
445	356	125	1	A
446	2 738	275	7	S/V
450	0	0	0	K
Paxlovid®				
144	2	0	0	M/F/A/G/Y
165	0	0	0	T
166	0	0	0	Q
172	0	0	0	Q/F
192	1	1	0	T/S/V

Table 1: Positions where mutations are known to result in escape from sotrovimab, cilgavimab, or Paxlovid®, their prevalence, and the specific amino acid mutations known to result in escape, July 2022. Note: defining mutations of the currently dominant Omicron lineages and are not shown. Only mutations enhancing escape in sublineages are shown.

The circulation of specific mutations leading to decreased effectiveness of known therapeutics available for clinical use in Switzerland will be surveilled (see Section 7), but their prevalence remains low.

Notably, there has been a substantial and worrying increase in Europe and the rest of the world in mutations

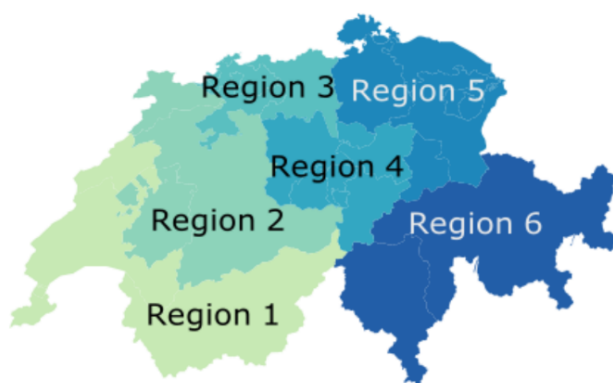
leading to escape from Cilgavimab (particularly at position 346) although, aside from the 3436T mutation, their presence in Switzerland remained low during the month of July.

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.

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 Nidwalden), 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>

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

During July, the FOPH reported a total of 172,238 confirmed SARS-CoV-2 cases in Switzerland, representing an increase from June. 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 48,339 positive tests during the surveilled program, which represents about 28% of the total number of cases reported in Switzerland (including both PCR and antigen-based tests). 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 supplementary 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 of 2,034 SARS-CoV-2 sequences have been declared to have been submitted to GISAID during this period. There are 2,119 sequences available for this period on GISAID as of 26 August 2022, and the difference may be explained by reporting delays and differences between collection/submission dates.

This represents around 1.18% 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 at the request of the Cantonal physician teams.

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
27	July 4 to July 10	598
28	July 11 to July 17	389
29	July 18 to July 24	630
30	July 25 to July 31	417
Total		2 034

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.

The total number of SARS-CoV-2 sequences declared and submitted to GISAID by each laboratory during this period 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 remained stable during July (weeks 27-30), while the fraction sequenced remained low. Since the beginning of this program, almost all of the sequences available, and on which the surveillance is conducted, come from the national surveillance program.

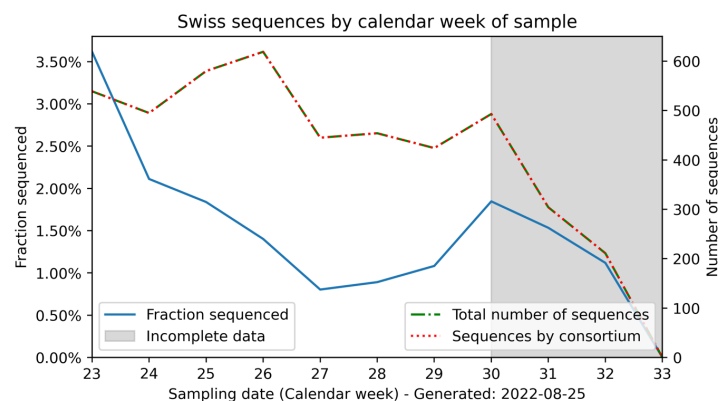


Figure 1: Number of SARS-CoV-2 sequences available for Switzerland (total available Swiss sequences in GISAID in green, Swiss sequences submitted through the program in dotted orange) and fraction of the total number of positive cases declared to the FOPH that have been sequenced (blue curve).

During the surveilled period, the absolute number of sequences generated remained fairly high, at hundreds of sequences per week. The total proportion of positive sequenced cases was less than 1% at the start of the month, but declining case numbers cause this proportion to rise to above 1.5% by the end of the month. These sequences include those from sites with hospitalized patients, and thus should be adequate for surveillance.

Figure 2 displays the number and fraction of SARS-CoV-2 cases sequenced for each Swiss region. Regions 4 and 6 had the lowest total number of sequences, while regions 4 and 3 had the lowest fraction of cases sequenced.

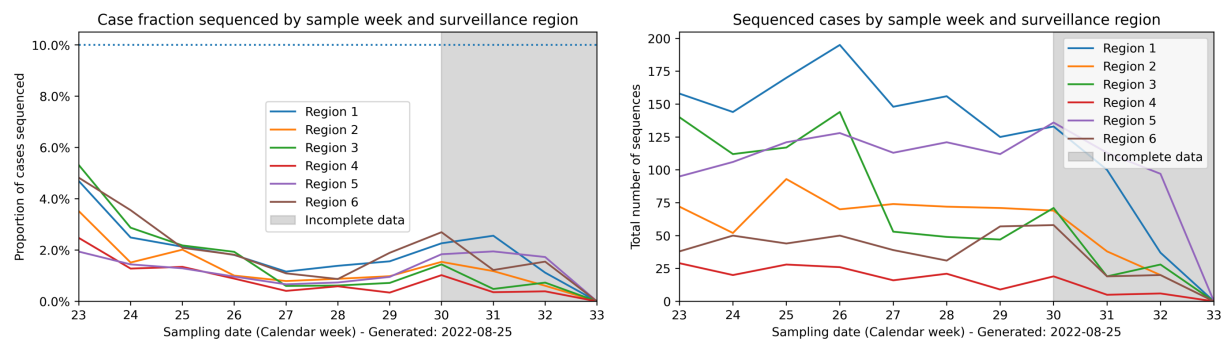


Figure 2: Sequencing coverage among the different Swiss regions per week, presented by fraction of cases sequenced (left) and by number of sequences (right).

5. Recently circulating variants in Switzerland as of June 2022

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).

Omicron BA.5 was by the most commonly retrieved lineage in July (Figures 3-5, Table 3). No BA.3 was found during the month of July. Delta and Omicron BA.1 have essentially disappeared, with 1 sequence each found in July. 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>. Notably, 1 BA.2.75 sequence was found in Ticino in the month of July.

Region	BA.1	BA.2	BA.2.12.1	BA.4	BA.5	Delta	None	other	sequences	cases	% sequenced
All	3	49	16	88	1345	2	79	234	1816	172238	1.1%
1	0	7	3	24	447	0	28	53	562	37879	1.5%
2	1	3	2	27	177	0	42	34	286	29260	0.98%
3	0	20	2	11	157	0	1	29	220	28238	0.78%
4	0	1	1	3	47	0	0	13	65	11997	0.54%
5	2	13	6	12	372	2	5	70	482	52568	0.92%
6	0	5	2	9	131	0	3	35	185	12296	1.5%

Table 3: number of sequences corresponding to selected variants in each region of Switzerland from 4 July 2022 to 31 July 2022, according to data received by 26 August, 2022. Sequences with poor coverage where lineages could not be assigned are listed as "None".

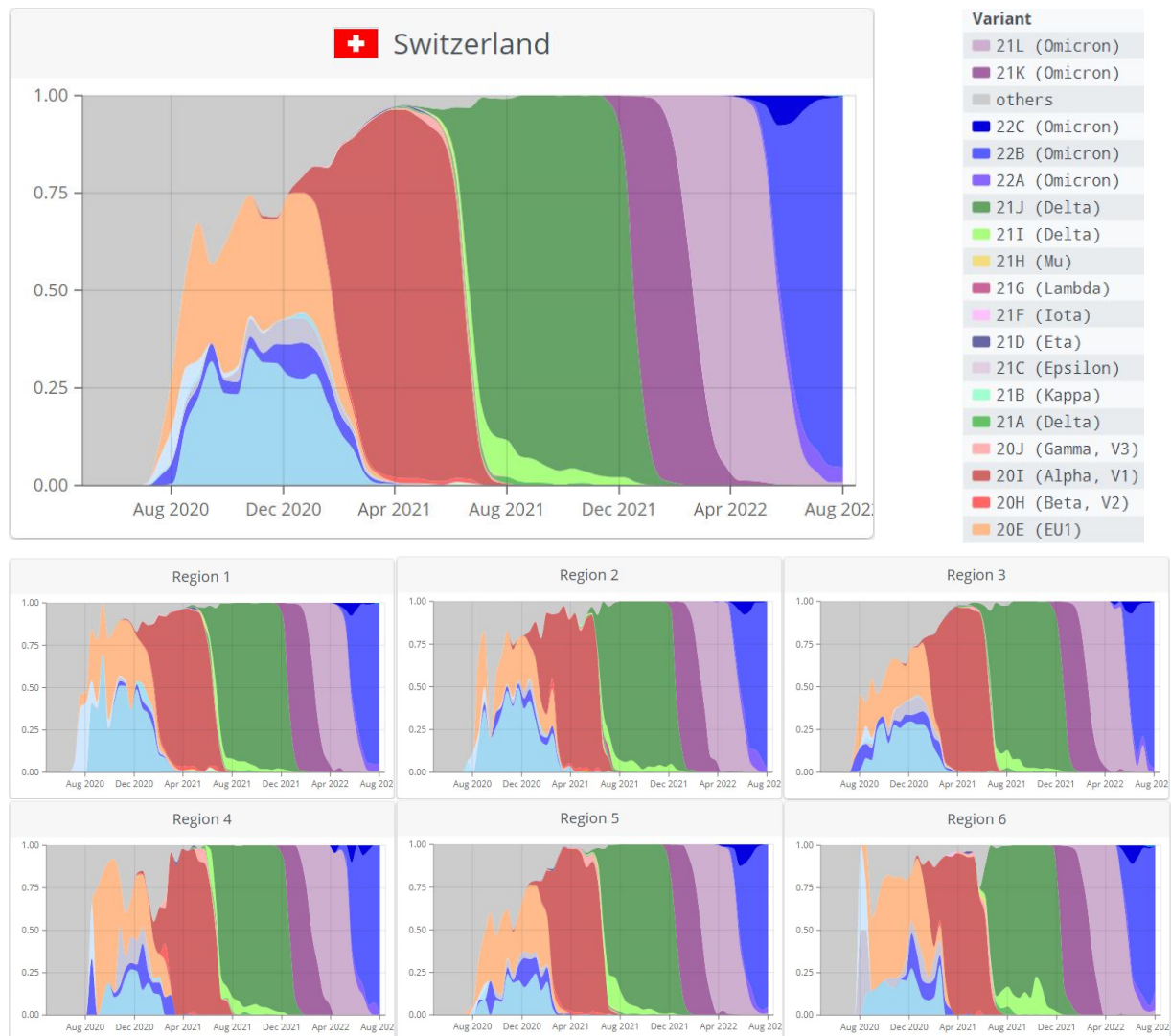


Figure 3: proportion of the total number of sequences (not cases), over time, that fall into defined variant groups, for Switzerland. Screenshot from CoVariants website. Dynamic navigation is available at <https://covariants.org/per-country>. Dark green indicates the B.1.617.2 (Delta) lineage or its sub-lineages. Dark Red indicates B.1.1.7 (Alpha). Purple/21K indicates Omicron BA.1, Light purple/21L indicates Omicron BA.2, which is currently dominant. Dark blue/22C indicates Omicron BA.2.12.1, while a faint blue/22B indicates Omicron BA.5 and a blueish-purple/22A indicates Omicron BA.4.

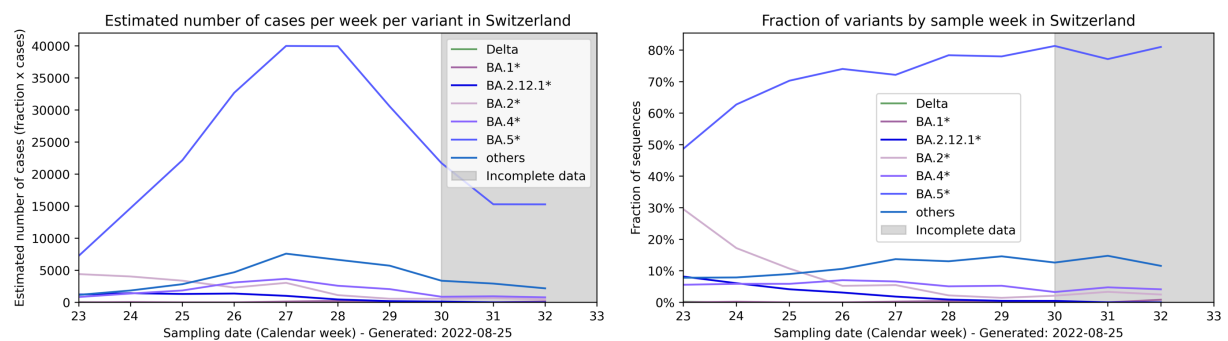


Figure 4: (Left): Percentage of circulating VOCs and VOIs in Switzerland by week, up to the 30 first weeks of 2022 (total number of BA.2, BA.2.12.1, BA.4, and BA.5 sequences from Switzerland and successfully submitted to GISAID are shown here). Note the grey shaded area indicates a period of incomplete data. (Right): Estimated number of sequences BA.2, BA.2.12.1, BA.4, and BA.5 retrieved during the surveilled period.

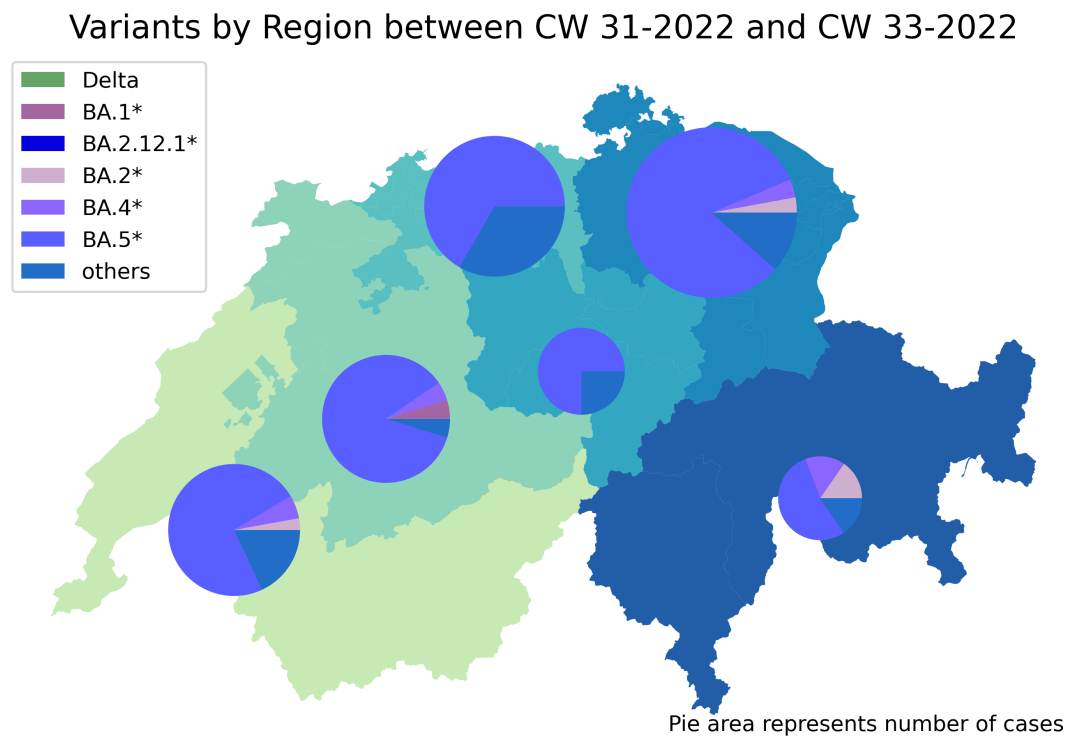


Figure 5: Distribution of variants per region, for the end of June 2022 shown on a map. The size of the pie chart corresponds to the total number of sequences. Note the large share of the share of the BA.5 lineage, in all regions as of the time of this report.

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 correctly predicted that Omicron would be the dominant SARS-CoV-2 variant in Switzerland. These models also correctly predicted that the BA.1 sub-lineage would be replaced by the BA.2 sublineage (Figure 6). In May, the analysis predicted that BA.2 would be displaced by other variants (mainly BA.5), which was indeed correct. Despite this track record of success, the current estimates have wide confidence intervals and it is currently unclear if BA.4 and 5 will be displaced by a BA.2 sublineage (specifically BA.2.75), another lineage entirely, or if it they (or one of their sublineages) will remain dominant.

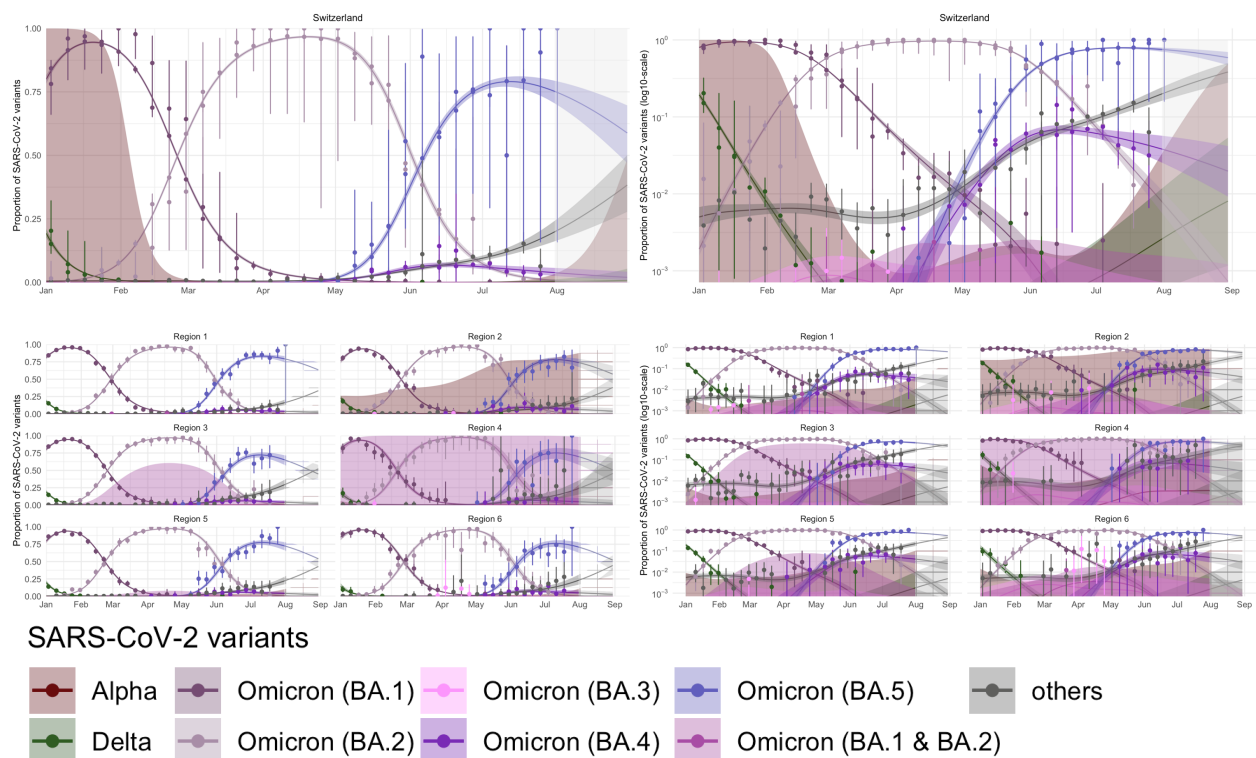


Figure 6: Observed and modeled proportion of SARS-CoV-2 variants over time in Switzerland. Left: graphed by linear proportions. Right: graphed by Log₁₀ proportions. Since early 2021, multiple successive variants have been observed to displace all previous variants (often achieving a dominance of >99.9% of the circulation). Alpha was replaced by Delta, followed by Omicron BA.1, then Omicron BA.2, and now Omicron BA.5. Model fits are based on a multinomial logistic regression with splines.

7. Surveillance of mutations associated with reduced mAb treatment efficacy

A number of mutations have been reported to result in significantly reduced *in vitro* effectiveness of the monoclonal antibodies used to treat patients in Switzerland. Notably, all Omicron lineages are completely resistant to neutralization by casirivimab/imdevimab. Sotrovimab retains substantial neutralizing activity against BA.1, but this neutralization is significantly decreased for BA.2/4/5 (and in particular, some of their sublineages). The escape is however not complete, and sotrovimab retains significant activity at higher titers – thus the frequencies of mutations (aside from lineage defining mutations) reported to escape neutralization by sotrovimab are still being followed (Table 4).

	337H		337L		337R		337T	
Dates	Global	Switzerland	Global	Switzerland	Global	Switzerland	Global	Switzerland
4.7 to 31.7	1	0 (Eur:1)	5	1 (Eur: 2)	2	1 (Eur: 1)	0	0

	340A		340K		340G		340Q	
Dates	Global	Switzerland	Global	Switzerland	Global	Switzerland	Global	Switzerland
4.7 to 31.7	11	1 (Eur: 5)	29	1 (Eur: 21)	1	0 (Eur: 1)	10	0 (Eur: 8)

	340V		356T		377K	
Dates	Global	Switzerland	Global	Switzerland	Global	Switzerland
4.7 to 31.7	1	0 (Eur: 1)	86	0 (Eur: 33)	0	0

Table 4: Global and Swiss counts of sequences bearing escape mutations from sotrovimab for July 2022

Evusheld®, which consists of a cocktail of 2 mabs, tixagevimab and cilgavimab, is also used in Switzerland. Tixagevimab is not effective against BA.2/4/5, although the BA.2.75 sublineage is neutralized by tixagevimab, likely due to a reversion mutation. Cilgavimab is able to neutralize BA.2/4/5, although its neutralization is reduced against BA.4/5, and eliminated in the BA.4.6/4.7/5.9 sublineages.

Mutations resulting in partial escape from cilgavimab are shown in table 5. As seen in tables 4&5, known mutations enabling escape from sotrovimab and Evusheld® have been detected in Switzerland, but remain rare. None of the sequences with escape mutations to sotrovimab come from patients originating from Geneva, but there are numerous cilgavimab escape mutation (1x 346S, 1x 444R, and 13x 346T). Notably, none of these patients have been treated with Evusheld: 2 (one with 2 escape mutations) immunosuppressed patients received sotrovimab, the rest were infected with variants already carrying the 346T mutation: 1x BF.7, 1x BA.4.6, 8 patients with BA.5.2.1 (7 from the same cluster). The 346T mutation is associated with the BA.4.6 and BA.5.2.1 sublineages and escape from humoral immunity, thus it is not expected to be seen only in response to mAb treatment.

	346I		346K		346S		346T	
Dates	Global	Switzerland	Global	Switzerland	Global	Switzerland	Global	Switzerland
4.7 to 31.7	987	6 (Eur: 743)	235	3 (Eur: 115)	710	6 (Eur: 345)	11 747	44 (Eur:3551)

	444E		444Q		444R		445A	
Dates	Global	Switzerland	Global	Switzerland	Global	Switzerland	Global	Switzerland
4.7 to 31.7	10	0 (Eur: 3)	2	0 (Eur: 1)	554	1 (Eur: 167)	356	1 (Eur: 125)

	446S*		446V		450K	
Dates	Global	Switzerland	Global	Switzerland	Global	Switzerland
4.7 to 31.7	2 676	7 (Eur: 241)	62	0 (Eur: 34)	0	0

Table 5: Global and Swiss counts of sequences bearing escape mutations from cilgavimab for July 2022: * 446S is a BA.1 associated mutation. Note: defining mutations of the Dominant BA.4/5 Omicron lineages and are not shown.

Paxlovid®, which inhibits the main viral protease encoded by the viral gene nsp5 is also used in Switzerland. In the absence of any treatment with Paxlovid®, escape mutations are not expected to produce any benefit, and the mutations are not linked to general antigenic shift like the escape mutations to the therapeutic mAbs (ie: sotrovimab and Evusheld®). This likely explains the scarcity of escape mutations against Paxlovid®. Mutations resulting in partial escape from Paxlovid® are shown in table 6.

	144M		144F		144A		144G	
Dates	Global	Switzerland	Global	Switzerland	Global	Switzerland	Global	Switzerland
4.7 to 31.7	0	0	0	0	2	0 (Eur: 0)	0	0

	144Y		165T		166Q		172Q	
Dates	Global	Switzerland	Global	Switzerland	Global	Switzerland	Global	Switzerland
4.7 to 31.7	0	0	0	0	0	0	0	0

	172F		192T		192S		192V	
Dates	Global	Switzerland	Global	Switzerland	Global	Switzerland	Global	Switzerland
4.7 to 31.7	0	0	0	0	0	0	1	0 (Eur: 1)

Table 6: Global and Swiss counts of sequences bearing escape mutations from Paxlovid®: Sequenced escape mutations remained extremely rare worldwide during the month of July.

8. Wastewater surveillance program

Sequences are obtained from six wastewater treatment plants (WWTPs) that are tested on a daily basis. During the month of June, BA.5 kept growing in relative abundance, to become almost fixed in most surveyed area during the month of July. After rising while BA.2 was still the dominating variant, the BA.4 variant has now declined and appears almost undetectable in waste water.

Quantification of BA.4 and BA.5 in sewage has exhibited some particular challenges. Those variants share most of their defining mutations with BA.2, which was the dominating variant at the time of their introduction and spread. The very limited number of discriminating mutations thus requires particular care in the wet lab protocols and computational methods used. However, although challenging, quantification is still possible.

BA.2.75 was first detected in samples from Geneva on June 22nd, and on June 23rd in samples from Zürich. Since then, detections of the variant have been more frequent.

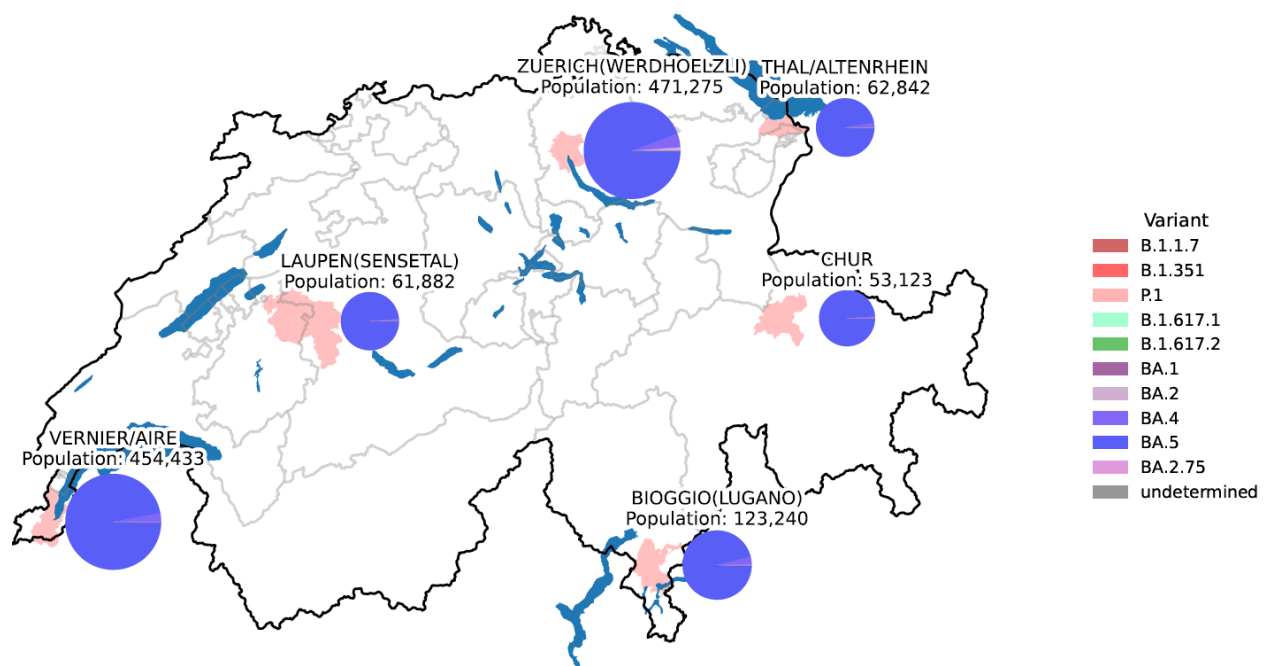


Figure 7:

Overview of the relative abundances of variants of SARS-CoV-2 at the end of July 2022, estimated from wastewater samples collected daily during the month 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 neighbouring French communities.

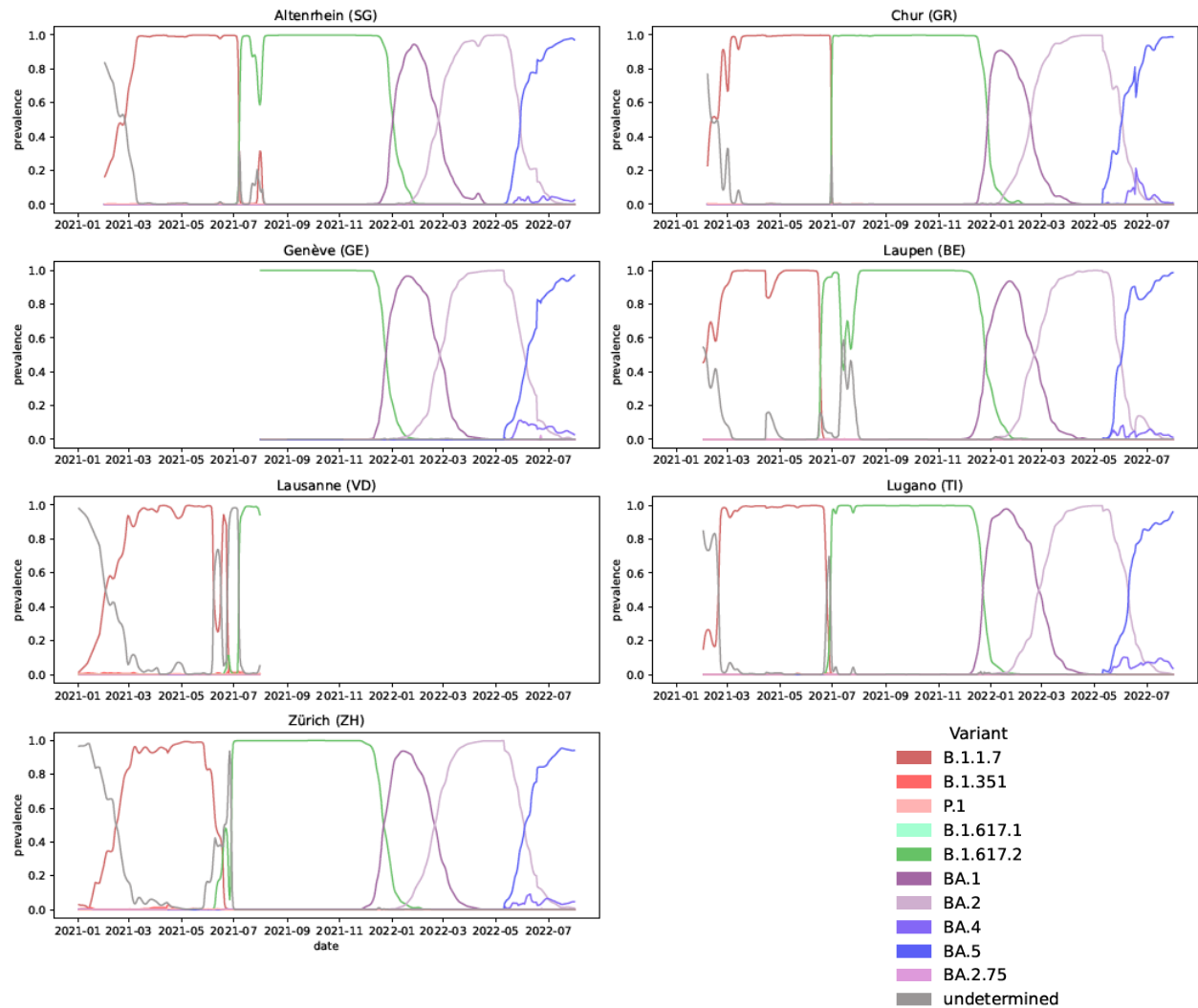


Figure 8: Relative abundances of variants of SARS- CoV-2 estimated from wastewater samples collected daily until July 31, 2022 (except Lausanne: July 31, 2021) in WWTPs located in 7 different Swiss cantons. An online dynamic navigation is available at <https://bsse.ethz.ch/cbg/research/computational-virology/sarscov2-variants-wastewater-surveillance.html>.

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

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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 in this table specifically cover the period from 4 July to 31 July 2022.



sup_table_overview
_Jul.xlsx

Supplementary Table 1: Epidemiological data for Switzerland, its regions and cantons for June: 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
27	July 4 to June 10	36 439	15 191	598	41.69%	3.94%
28	July 11 to June 17	30 425	14 108	389	46.37%	2.76%
29	July 18 to June 24	24 426	11 397	630	46.66%	5.53%
30	July 25 to June 31	19 477	8 045	417	41.31%	5.18%
	Total	110 767	48 741	2 034	44.00%	4.17%

Supplementary Table 2: Total number of tests performed by the laboratories participating in the surveillance program from 4 July to 31 July 2022.

Week	Date	Basic Surveillance				Augmented Surveillance						Sentinella Laboratories		
		EOC	Labor Team W	Risch	SRO	USB	IFIK	Diana labs	CHUV	UZH	ICH-VS*	HUG	ETH/ Viollier	All
27	July 4 to June 10	26	20	58	28	36	77	0	36	86	44	110	77	598
28	July 11 to June 17	18	29	56	0	40	0	43	41	84	0	0	78	389
29	July 18 to June 24	24	22	46	28	40	74	0	33	80	45	142	96	630
30	July 25 to June 31	24	24	11	0	40	0	47	38	88	0	0	145	417
	Total	92	95	171	56	156	151	90	148	338	89	252	396	2 034

*Supplementary Table 3: number of sequences submitted to GISAID by each laboratory during the surveilled period (4 July to 31 July 2022). *including sequencing sent to high-throughput platforms.*

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