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

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1. Summary

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

In the midst of increasing case numbers, approximately 1.9% of the total number of cases identified in Switzerland in June were sequenced by the Surveillance program, yielding over 2,300 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.

Notably, the BA.4/5 variants bring with them resistance to the antibody therapies of Evusheld® (complete resistance to tixagevimab, partial resistance to cilgavimab) and sotrovimab. BA.5 substantially escapes immunity from vaccination and previous infections, but previous BA.1 and BA.2 do infections confer better protection. *In vitro* and animal data suggests that BA.5 is intrinsically more severe than BA.1 and BA.2. This is likely to be mitigated to some extent by the protective effects of vaccination and previous exposure to BA.1 and BA.2 but most importantly the BA.4/5 wave did not result in a large increase of hospitalizations in Switzerland.

The BA.2.12.1 sub-variant, which became the dominant variant in the USA (and has already been replaced by BA.4/5 there), was detected 145 times in Switzerland during the month of June. It is unlikely to be a cause for concern and do not have a transmissibility advantage compared to BA.4/5. The circulation of BA.1 and its subvariants was extremely low in June, with only 22 sequences detected. Delta circulation has effectively stopped in Switzerland, with only 1 sequence detected in June, originating from someone with a chronic infection.

The BA.2.75 sub-variant, which is currently growing fast in India, has been detected only in Swiss waste-water but not in patient samples including in the national genomic surveillance program. Preliminary data from India suggest a competitive advantage of BA.2.75 over BA.4/5. However, it is still unclear if it will outcompete BA.5. It must be noted that the immunological background of the Swiss and Indian populations are now quite different. This variant will be the subject of close scrutiny.

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 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. 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 May 30 to July 3, 2022 (weeks 22, 23, 24, 25, 26). 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.

A BA.2 sublineage, BA.2.12.1, with an L452Q (as opposed to R, which is found in BA.4/5 and Delta) briefly achieved dominance in the USA, but it too has been replaced by BA.4 and BA.5.

Another sublineage of BA.2, BA.2.75 has been growing rapidly in India, where BA.4/5 circulation has remained low. Notably, sequencing coverage in India is lower than in many western countries. BA.2.75 has 8 Spike mutations relative to BA.2. In contrast BA.4/5 have just 2 amino acid mutations and 2 deleted amino acids, thus BA.2.75 is the most divergent Omicron variant with significant circulation. A recent study suggests that BA.2.75 escapes immunity raised against Delta infections better than any other variant. Notably India was the origin of the Delta variant and had the highest Delta infection rates. Furthermore, BA.4/5 share the L452R mutation in the receptor binding domain with Delta. No sign of growth has been seen outside of India, and it is too early to predict if BA.2.75 can displace BA.5 – its growth in India may be a result of India's unique epidemiological history. In contrast, 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.

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.

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. Early data suggests low neutralization of BA.4/5 by sera from

BA.1 and, somewhat surprisingly, BA.2 vaccine-breakthrough infections. While all Omicron sublineages largely escape humoral immunity, cell mediated immunity remains mostly intact.

A 3rd vaccine dose or a combination of previous infection and 2 vaccine doses has been shown to retain moderate neutralization of BA.1 and BA.2, but neutralizing titers are very low against BA.4 and 5. Efficacy preventing hospitalization and death is reduced but remains high. Four doses have been shown to be even more effective: Israeli studies investigating the effect of a 4th dose have found that vaccine efficacy against any infection, relative to a 3rd dose, was relatively low at 30%. Vaccine efficacy of a 4th dose against symptomatic disease was found to be substantially higher, possibly as high as 65%. Updated bivalent vaccines using the Omicron BA.1 sequence performed much better against the currently circulating BA.2/5/5 subvariants, but neutralization was still reduced relative to BA.1

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. 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. While BA.2 was more severe than BA.1 in an animal study, no clinical difference between BA.1 and BA.2 infections has been noted.
BA.4 and BA.5 have apparently regained the ability to use TMPRSS2 mediated entry pathways, 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 June.

Recombinants
Recombinant virus formation occurs by coinfection by 2 different strains within the same host. While numerous verified recombinants have been verified, so far there has been no sign that any of them will outcompete BA.4 or 5.

Therapeutic intervention effectiveness
All sublineages display complete escape from combination of casirivimab/imdevimab. Sotrovimab is currently the only antibody available in Switzerland that retains substantial neutralizing activity against BA.1, although 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: one study reports BA.2.75 is significantly more susceptible to sotrovimab, while another reports 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. Notably, BA.2.75 contains an escape mutation against cilgavimab associated with up to a 12 fold reduction in neutralization.

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). 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	5	3	0	R/L/H/T
340	116	101	4	K/A/G/Q/V
356	95	75	1	T
377	0	0	0	K
Cilgavimab				
346	592	475	30	I
371	393 008	165 877	2 434	F
444	241	75	1	R/Q/E
445	119	47	1	A
446	957	252	2	S/V
450	1	1	0	K
452	207 805	117 130	1 764	R
Paxlovid®				
144	0	0	0	M/F/A/G/Y
165	0	0	0	T
166	0	0	0	Q
172	0	0	0	Q/F
192	2	0	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, June 2022. Note: 484A and 655Y are defining mutations of all Omicron lineages and are not shown. 371F is a mutation in Omicron BA.2,4, and 5. 452R is a standard BA.4/5 mutation

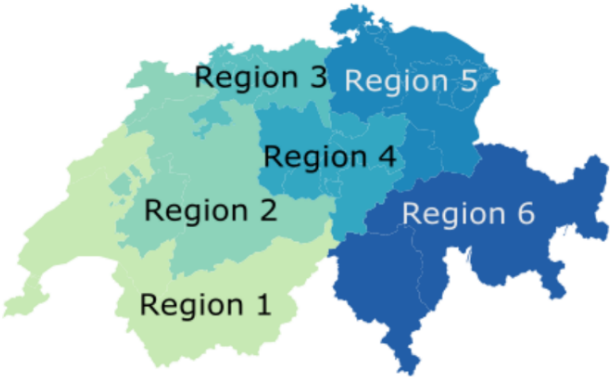
The circulation of specific mutations leading to decreased effectiveness of known therapeutics available for clinical use in Switzerland will be surveilled (see Section 7), but their prevalence remains low.

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 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

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

During June, the FOPH reported a total of 124,184 confirmed SARS-CoV-2 cases in Switzerland, representing a significant increase from May. 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 36,457 positive tests during the surveilled program, which represents about 29% 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 2,379 SARS-CoV-2 sequences have been declared to have been submitted to GISAID during this period. There are 2,523 sequences are available for this period on GISAID as of 26 July 2022, and the difference may be explained by reporting delays and differences between collection/submission dates.

This represents around 1.9% 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
22	May 30 to June 5	442
23	June 6 to June 12	571
24	June 13 to June 19	365
25	June 20 to June 26	616
26	June 27 to July 3	385
	Total	2 379

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 June (weeks 22-26), while the fraction sequenced steeply decreased, reflecting a steep increase in case numbers. Since the beginning of this program, almost all of the sequences available in GISAID (green curve) and those on which the surveillance is conducted, come from the national surveillance program.

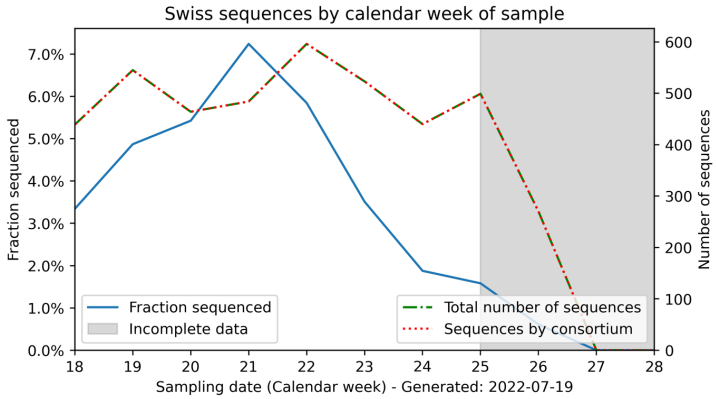


Figure 1: Number of SARS-CoV-2 sequences available for Switzerland (total available Swiss sequences in GISAID in green, Swiss sequences submitted through the program in dotted orange) and fraction of the total number of positive cases declared to the FOPH that have been sequenced (blue curve).

During the surveilled period, the absolute number of sequences generated remained fairly high, at hundreds of sequences per week. The total proportion of positive sequenced cases was 7% at the start of the month, but rising case numbers cause this proportion to drop to just above 1% 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 3, 4, and 5 had the lowest fraction of cases sequenced.

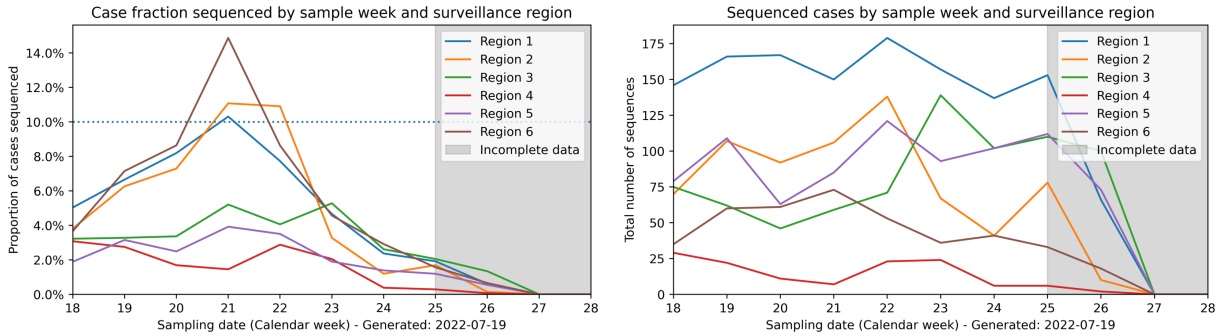


Figure 2: Sequencing coverage among the different Swiss regions per week, presented by fraction of cases sequenced (left) and by number of sequences (right).

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 June (Figures 3-5, Table 3). No BA.3 was found during the month of June. Delta an Omicron BA.1 have essentially disappeared, with 1 and 2 sequences respectively found in June. 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.

Region	BA.1	BA.2	BA.2.12.1	BA.4	BA.5	Delta	None	other	sequences	cases	% sequenced
All	2	505	145	155	1422	1	45	179	2454	124184	1.98%
1	2	159	27	45	448	0	5	32	718	30221	2.38%
2	0	69	20	26	195	0	1	24	335	18327	1.83%
3	0	112	30	32	318	0	15	47	554	21098	2.63%
4	0	14	4	4	32	0	0	10	64	8551	0.75%
5	0	98	47	33	294	1	18	54	545	38337	1.42%
6	0	46	16	13	109	0	6	11	201	7650	2.63%

Table 3: number of sequences corresponding to selected variants in each region of Switzerland from 30 May 2022 to 03 July 2022, according to data received by 22 July, 2022. Sequences with poor coverage where lineages could not be assigned are listed as "None".

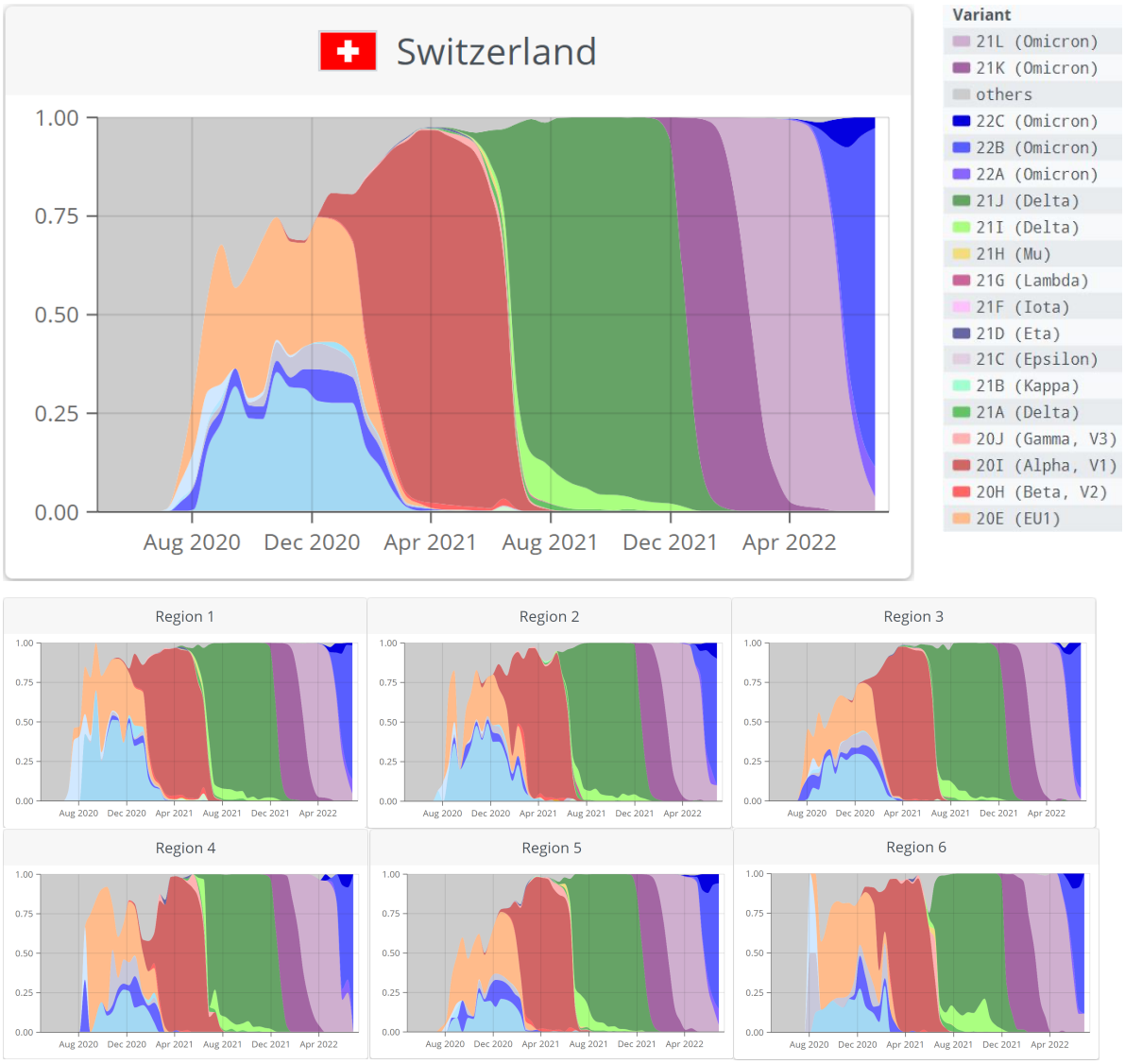


Figure 3: proportion of the total number of sequences (not cases), over time, that fall into defined variant groups, for Switzerland. Screenshot from CoVariants website. Dynamic navigation is available at https://covariants.org/per-country. Dark green indicates the B.1.617.2 (Delta) lineage or its sub-lineages. 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. Bright 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.

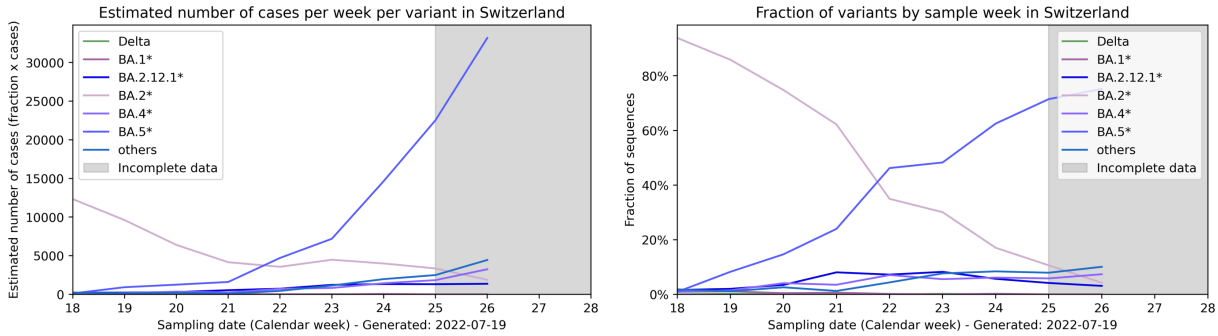


Figure 4: (Left): Percentage of circulating VOCs and VOIs in Switzerland by week, up to the 25 first weeks of 2022 (total number of BA.2, BA.2.12.1, BA.4, and BA.5 sequences from Switzerland and successfully submitted to GISAID are shown here). Note the grey shaded area indicates a period of incomplete data.
(Right): Estimated number of sequences BA.2, BA.2.12.1, BA.4, and BA.5 retrieved during the surveilled period.

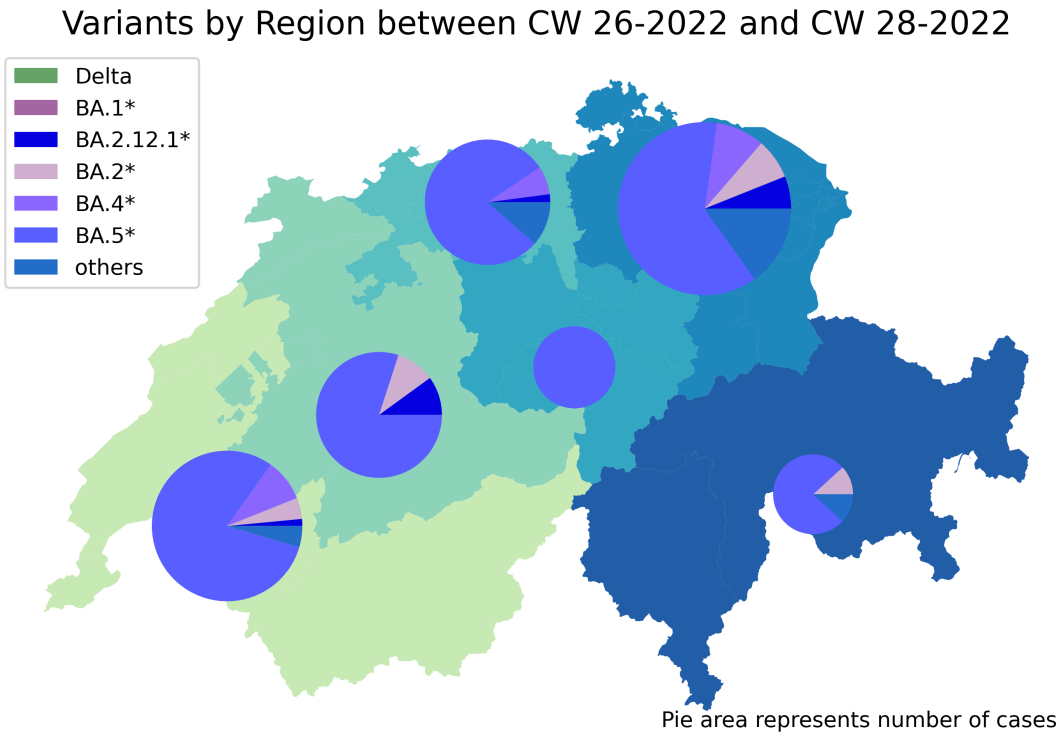


Figure 5: Distribution of variants per region, for the end of June 2022 shown on a map. The size of the pie chart corresponds to the total number of sequences. Note the large share of the share of the BA.5 lineage, in all regions as of the time of this report.

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.

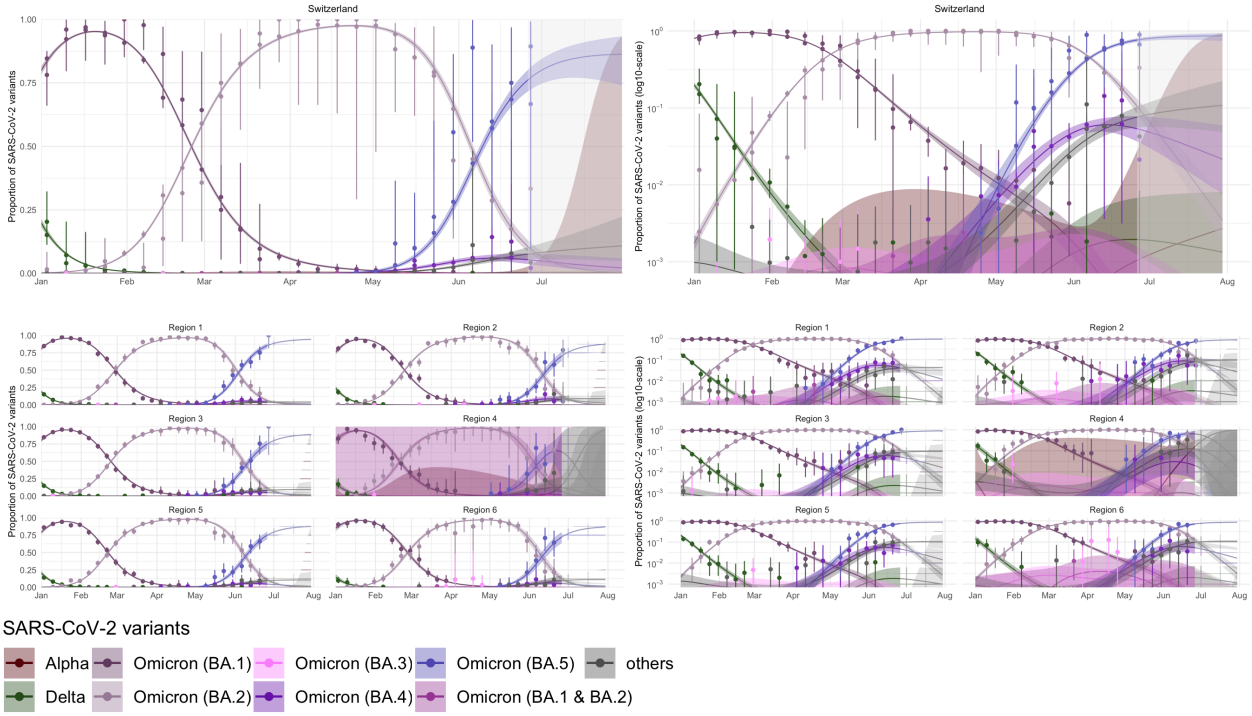


Figure 6: Observed and modeled proportion of SARS-CoV-2 variants over time in Switzerland. Left: graphed by linear proportions. Right: graphed by Log_{10} proportions. Since early 2021, multiple successive variants have been observed to displace all previous variants (often achieving a dominance of >99.9% of the circulation). Alpha was replaced by Delta, followed by Omicron BA.1, then Omicron BA.2. It now appears these will be replaced by 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 sotrovimab and casirivimab/imdevimab association monoclonal antibodies used to treat patients in Switzerland. Notably, Omicron is completely resistant to neutralization by casirivimab/imdevimab, and sotrovimab remains the only mAb available in Switzerland that retains effectiveness against Omicron BA.1. Unfortunately, this effectiveness is expected to be significantly decreased for other Omicron sub-lineages, on the basis of various experiments strong reductions of *in vitro* neutralizing titers. The escape is however not complete, and sotrovimab retains significant activity against BA.2 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
30.5 to 3.6	0	0	3	0	2	0	0	0

	340A		340K		340G		340Q	
Dates	Global	Switzerland	Global	Switzerland	Global	Switzerland	Global	Switzerland
30.5 to 3.6	9	0	63	2	0	0	39	1

	340V		356T		377K	
Dates	Global	Switzerland	Global	Switzerland	Global	Switzerland
30.5 to 3.6	5	1	95	1	0	0

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

Evusheld®, which consists of a cocktail of 2 mabs, tixagevimab and cilgavimab, is also used in Switzerland. Tixagevimab is not effective against BA.2, nor the newer emerging variants, but cilgavimab is expected to retain efficacy against BA.2. It is already known to have reduced neutralizing capacity against BA.4/5, and reports about neutralizing capacity against BA.2.12.1 are mixed. 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. Notably, 3 of 5 sequences with escape mutations come from patients originating from Geneva (1x 346I, 1x 356T, and 1x 444R). All 3 patients were immunosuppressed. One patient known to have a chronic BA.2 infection was treated by sotrovimab, and one received sotrovimab as prophylaxis approximately 4 months prior to infection by BA.5.

	346I		371F*		444R		444Q	
Dates	Global	Switzerland	Global	Switzerland	Global	Switzerland	Global	Switzerland
30.5 to 3.6	592	30	393 008	2 434	231	1	1	0

	444E		445A		446S**		446V	
Dates	Global	Switzerland	Global	Switzerland	Global	Switzerland	Global	Switzerland
30.5 to 3.6	9	0	119	1	923	2	34	0

	450K		452R***	
Dates	Global	Switzerland	Global	Switzerland
30.5 to 3.6	1	0	207 805	1 764

*Table 5: Global and Swiss counts of sequences bearing escape mutations from cilgavimab: * 371F is a defining mutation of BA.2, BA.4, and BA.5. It is associated with a 5 fold reduction in neutralization. ** 446S is a BA.1 associated mutation. *** 452R is a defining mutation of BA.4, and BA.5. It is associated with a 5-6 fold reduction in neutralization. Note: 484A and 655Y are defining mutations of all Omicron lineages and are not shown. They are associated with a 5-12 fold reduction in neutralization.*

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
30.5 to 3.6	0	0	0	0	0	0	0	0

	144Y		165T		166Q		172Q	
Dates	Global	Switzerland	Global	Switzerland	Global	Switzerland	Global	Switzerland
30.5 to 3.6	0	0	0	0	0	0	0	0

	172F		192T		192S		192V	
Dates	Global	Switzerland	Global	Switzerland	Global	Switzerland	Global	Switzerland
30.5 to 3.6	0	0	0	0	2	0	0	0

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

8. Wastewater surveillance program

Sequences are obtained from six wastewater treatment plants (WWTPs) that are tested on a daily basis. During the month of May, the BA.4 and BA.5 variants relative abundance rose rapidly, replacing the previously dominating BA.2. The BA.5 variant was almost dominating or dominating by the end of the month in most of the surveyed areas. During the month of June, BA.5 kept growing in relative abundance to become almost fixed in most surveyed area. The BA.4 variant on the other hand declined. The rise of BA.4 and BA.5 as seen in wastewater indicate growth rates per day comparatively to BA.2 of 0.060 (0.053 – 0.067) and 0.091 (0.086 – 0.097), respectively.

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 detected in the samples from Geneva on June 22nd, with a possible second detection on June 23rd in a sample from Zürich.

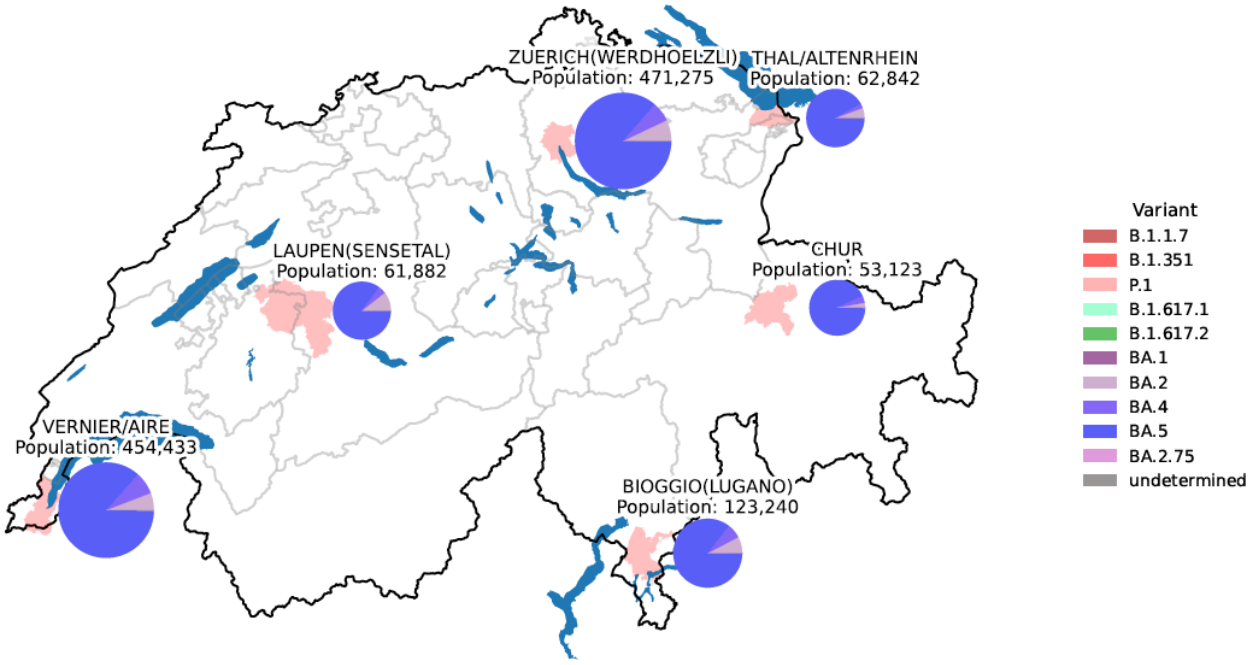


Figure 7:
Overview of the prevalence of variants of SARS-CoV-2 at the end of June 2022, estimated from wastewater samples collected daily during the month in WWTPs located in 6 different Swiss locations. Pie chart areas are proportional to population connected to the wastewater treatment plants. Pink shaded areas represent catchment areas (boundaries from 2017). The population connected to Vernier (GE) wastewater treatment plant also includes ~44,000 inhabitants from neighbouring French communities.

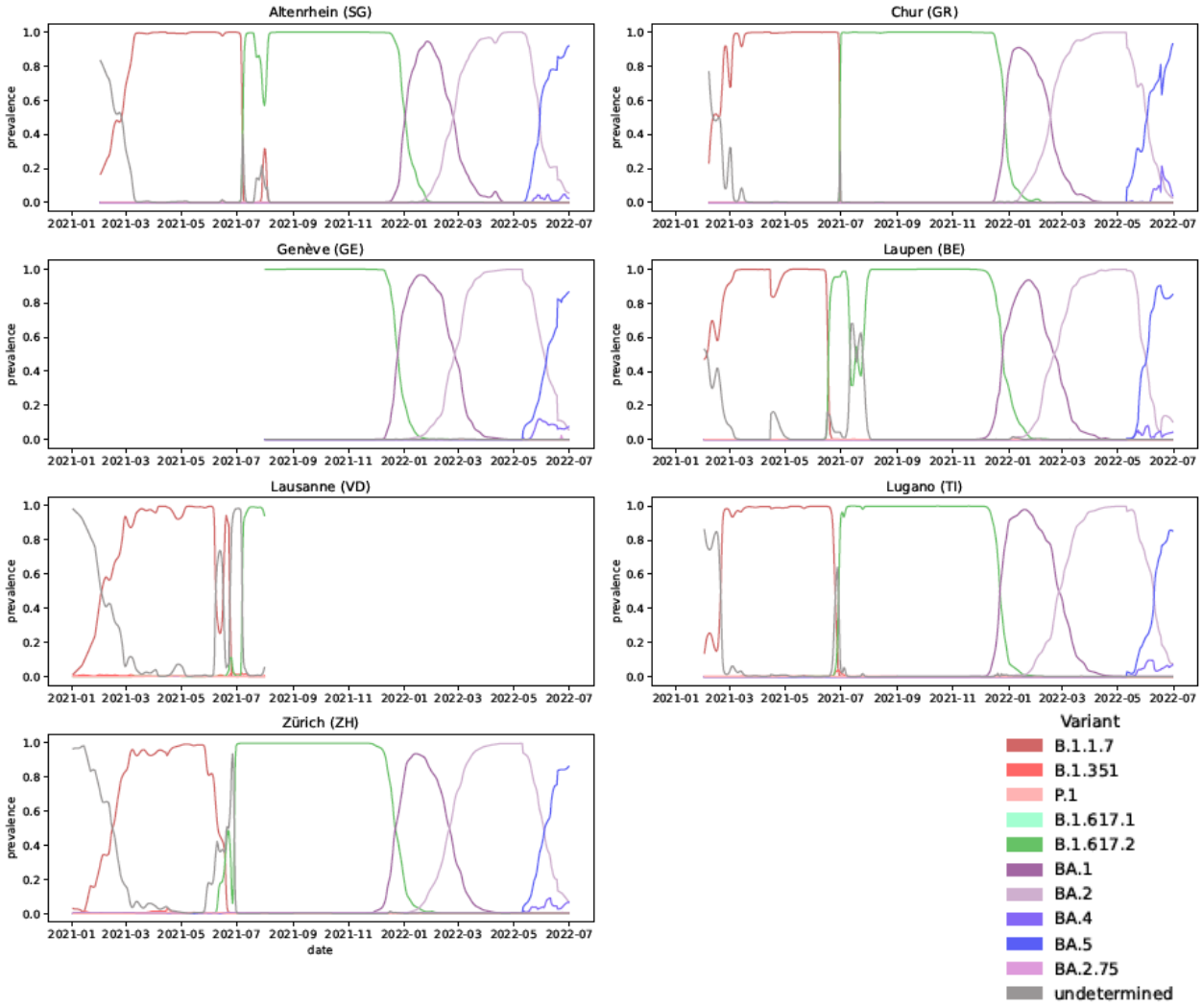


Figure 8: Prevalence of variants of SARS- CoV-2 estimated from wastewater samples collected daily until May 31, 2022 (except Lausanne: July 31, 2021) in WWTPs located in 7 different Swiss cantons. An online dynamic navigation is available at https://bsse.ethz.ch/cbg/research/computational-virology/sarscov2-variants-wastewater-surveillance.html.

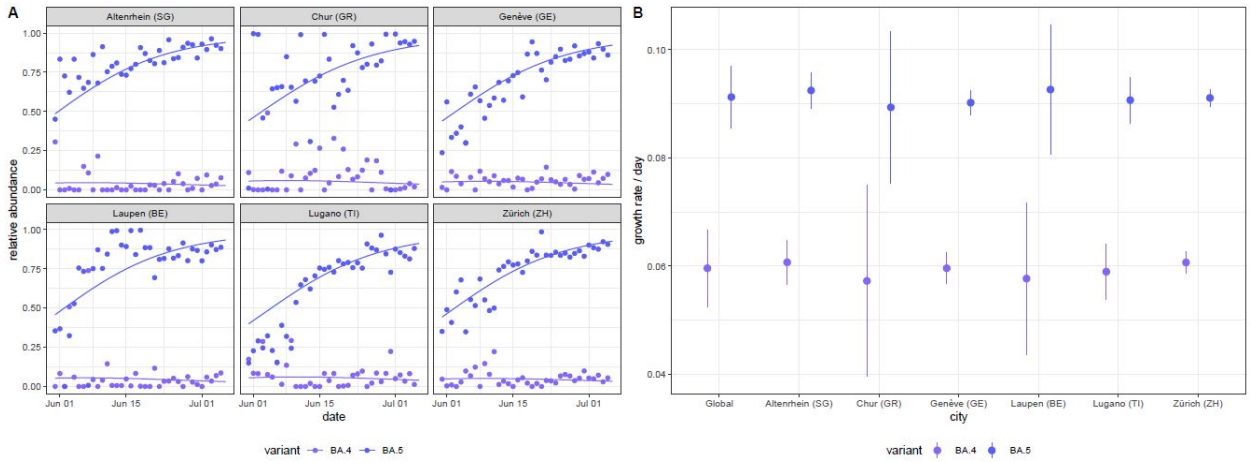


Figure 9: Logistic growth of BA.4 and BA.5 during the month of June in the surveyed wastewater treatment plants, fitted with a hierarchical multinomial growth model. A: fitted curves to the daily estimates of the variant prevalences. B: point estimates and confidence intervals of the logistic growth parameters, for the different treatment plants, as well as a pooled estimate (Global).

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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 5 June 2022 to 26 June 2022.

sup_table_overview_Jun.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
22	May 30 to June 5	12 628	3 114	442	24.66%	14.19%
23	June 6 to June 12	13 239	4 291	571	32.41%	13.31%
24	June 13 to June 19	17 688	6 859	365	38.78%	5.32%
25	June 20 to June 26	22 596	9 729	616	43.06%	6.33%
26	June 27 to July 3	30 313	12 464	385	41.12%	3.09%
	Total	96 464	36 457	2 379	37.79%	6.53%

Supplementary Table 2: Total number of tests performed by the laboratories participating in the surveillance program from 30 May 2022 to 3 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
22	May 30 to June 5	32	30	41	0	40	0	48	30	34	0	87	100	442
23	June 6 to June 12	23	17	57	0	40	66	0	41	40	40	150	97	571
24	June 13 to June 19	26	27	36	0	40	0	42	38	72	0	0	84	365
25	June 20 to June 26	25	23	57	29	0	79	0	39	85	41	163	75	616
26	June 27 to July 3	23	25	58	0	40	0	45	43	66	0	0	85	385
	Total	129	122	249	29	160	145	135	191	297	81	400	441	2379

*Supplementary Table 3: number of sequences submitted to GISAID by each laboratory during the surveilled period (30 May to 3 July 2022). *including sequencing sent to high-throughput platforms.*

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