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

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1. Summary

In September, COVID-19 cases numbers remained low and relatively stable in Switzerland, with vast majority of cases still caused by BA.5 or its sublineages.

Approximately 3.1% of the total number of cases identified in Switzerland in September were sequenced by the Surveillance program, yielding over 2'500 sequences. The vast majority of the sequences in Switzerland belong to BA.5 – BA.2.75 sublineages were rarely seen.

The currently circulating BA.5 variants are at least partially resistant to all the monoclonal antibody therapies used in Switzerland. In particular they are resistant to Evusheld®, which is composed of tixagevimab (complete resistance) and cilgavimab (partial resistance); and sotrovimab, for which the clinical effectiveness is unclear. BA.2.75, in contrast, displays high resistance to cilgavimab, but is susceptible to tixagevimab as lacks a spike 486 mutation present in BA.4/5 that leads to complete escape. However, the newer BA.2.75.2 sublineage does have such a mutation.

BA.4 and 5 sublineages with Spike 346 mutations enabling complete escape from cilgavimab (thus, complete escape from Evusheld®) are growing in frequency. In contrast, BA.2.75 sublineages (which may have complete escape from Evusheld®) are only rarely detected in Switzerland, and have no significant signs of local growth. In September, these resistant variants represented over 14% of the sequences identified in Switzerland. Importantly, this proportion was nearly 18% during the last 2 weeks of September, and preliminary data for October shows a proportion greater than 30% as of the time of this report. **There is a clear and present danger that all available monoclonal antibodies available in Switzerland will soon be ineffective against the majority of circulating variants. In particular, the current increase in BQ.1.1 and XBB is of concern as they will likely be dominant in Switzerland by the end of the year.**

The escape from immunity derived from vaccination or previous exposure by these subvariants is weaker than the escape seen against the monoclonal antibodies, but still substantial. While the bivalent BA.1 booster is not ideal and would benefit from a further update, available data suggests that it will perform significantly better than the previous vaccines against the currently circulating variants. Most importantly these subvariants have so far not resulted in a large increase of hospitalizations.

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, Erik Studer, Oluwaseun Oyewole, 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 29 August to 2 October, 2022 (weeks 35, 36, 37, 38, 39). 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---24-august-2022).

Omicron

The Omicron VOC (B.1.1.529) is characterized by a high divergence in the spike protein, which has allowed it to substantially escape immunity conferred by vaccination (using the original Wu-1 sequence) and prior infection with pre-Omicron variants. This VOC currently has 3 sublineages that still have significant circulation: BA.2,4, and 5, all of which have further "sub-sublineages". Despite all being considered "Omicron", these sublineages may differ from each other (in terms of mutation counts) more than the earlier VOCs differed from the original Wu-1 strain.

Notably, this is the first VOC to have subvariants causing multiple successive waves, arguing for treating Omicron subvariants as distinct VOCs. These sublineages have successively replaced each other, with BA.5 currently being dominant.

While BA.5 replaced BA.2, highly derived BA.2 sublineages have appeared, in particular, BA.2.75. Growth signals outside of India were initially small, but further observation has confirmed that this variant seems to outcompete "basic" BA.4 and 5.

Subvariants of BA.4 and BA.5 containing additional mutations, particularly at position 346 or 444 of the spike protein (such as BQ.1 and BA.4.6), seem to confer a growth advantage and enable complete escape from cilgavimab, rendering it fully resistant to Evusheld®. In particular, BA.Q.1.1 with the R346T mutation has strong signs of growth in many western countries. Some of these BA.4 and 5 subvariants seem to be more competitive than BA.2.75 and its sublineages.

BA.2.75 is likewise spawning subvariants, in particular BA.2.75.2, which has a spike 486 mutation enabling complete escape from tixagevimab. BA.2.75 subvariants also seem to be picking up 346 mutations enabling complete escape from cilgavimab.

A recombination event between a BA.5 sublineage (BJ.1) and a BA.2.75 sublineage (BM.1.1.1) has produced the XBB lineage, which is also showing strong signs of growth and immune escape.

Detection

All sub-lineages are still detected by RT-PCR tests, and all except BA.2 exhibit S-gene target failure with the Roche PCR assays regularly used in Switzerland. Given the current virus circulating, the absence of S-gene target failure is currently a good proxy for BA.2.75 infection. Likewise, its presence is indicative of a likely BA.5 (or BA.5 subvariant) infection. Further discrimination between subvariants is not feasible at this time by any method other than genomic sequencing.

Antigenic tests are still able to detect these variants, and sensitivity to the currently circulating variants is relatively unchanged relative to the initial virus. 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. Escape from monoclonal antibodies is extensive and is covered by the "Therapeutic intervention effectiveness" section.

Data suggests low neutralization of BA.2.75 and BA.4/5 by sera from BA.1 and BA.2 vaccine-breakthrough infections. BA.4 and BA.5 sublineages containing further escape mutations have been shown to be substantially less neutralized (>3x) than earlier variants by patient sera, even if the sera comes from

people exposed to “basic” BA.4 or BA.5. Similarly, the BA.2.75.2 sublineage neutralization titers were 6.5x lower than the neutralization titers for BA.5. Furthermore, these sublineages completely escape neutralization by Evusheld® and have substantially reduced neutralization by sotrovimab.

While all Omicron sublineages largely escape humoral immunity from pre-omicron vaccines and infections, cell mediated immunity remains mostly intact.

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. The efficacy of four doses 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 and sublineages, but neutralization was still reduced by approximately 3-fold relative to BA.1. Similarly, bivalent vaccines with BA.1 and in particular BA.5 did improve neutralization of BA.2.75, although the neutralization was still reduced relative to BA.1 and BA.5 respectively. Unlike the monoclonal antibody situation, neutralization capacity of patient sera against new variants is expected to gradually decline rather than suffer sharp drops in or complete loss of efficacy. Still, it is clear that additional updates would be very beneficial.

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 partial explanation for observations of the infections being less severe. 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.
Other studies of chimeric viruses (the ancestral virus with its spike replaced by an Omicron Spike) in mice suggest that the reduced severity is not due to properties of the spike protein and receptor usage/entry pathway. Notably, all Omicron lineages contain a T9I mutation in the E gene, which has been implicated in reduced severity.
There are conflicting animal studies with regards to the question of intrinsic severity, and 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.

Therapeutic intervention effectiveness
All sublineages display complete escape from combination of casirivimab/imdevimab. A matched cohort study found a noticable 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. In contrast a study done in the USA found a beneficial effect for both BA.1 and BA.2, although it had significant limitations specifically regarding its BA.2 conclusions. Currently, there is conflicting data regarding the efficacy of sotrovimab against BA.2.75, with reports variously indicating that its sensitivity is relatively unchanged or decreased relative to BA.5. 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. Additional spike 346 mutations seen in BA.4/5 sublineages lead to complete escape from cilgavimab, and these appear it is likely that cilgavimab will lose any efficacy that it still had as these sublineages become the dominant BA.4/5 sublineages.

Interestingly, while BA.2.75 contains an escape mutation against cilgavimab associated with up to a 12-fold reduction in neutralization, it lacks the spike 486 escape mutation of BA.4/5 and is susceptible to

tixagevimab. The overall effect is only a modest reduction in neutralizing activity by Evusheld® against BA.2.75 relative to BA.2, and a substantial improvement relative to BA.4/5.

Unfortunately, BA.4, BA.5, and BA.2.75 have formed sublineages that are outcompeting their parent strains, which contain additional escape mutations. Although BA.2.75 is susceptible to tixagevimab, BA.2.75.2 in particular has mutations resulting in a complete escape from tixagevimab. Similarly spike 346 mutations, which confer complete escape from cilgavimab in the BA.4 and 5 sublineages, are seen in BA.2.75, BA.4, and BA.5 sublineages. Notably, these lineages include BQ.1.1 (a BA.5 sublineage), and BA.2.75.2 – both these lineages are expected to completely escape Evusheld, and are outcompeting their parent lineages.

As sotrovimab and tixagevimab/cilgavimab are still 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 E166Q. 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 these mutations are favorable. 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	0.00%	0.00%	0.00%	R/L/H/T
340	0.02%	0.03%	0.04%	K/A/G/Q/V
356	0.55%	0.46%	0.29%	T
377	0.00%	0.00%	0.00%	K
Cilgavimab				
346	16.26%	17.53 %	15.62%	I/K/S/T
444	0.84%	0.82%	0.54%	E/Q/R
445	0.74%	0.61%	0.50%	A
446	2.59%	1.86%	2.46%	S/V
450	1.04%	1.24%	1.63%	K/D
Paxlovid®				
144	1	0	0	M/F/A/G/Y
165	0	0	0	T
166	1	0	0	Q/V
167	0	0	0	F
172	0	0	0	Q/F
192	1	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, August 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.

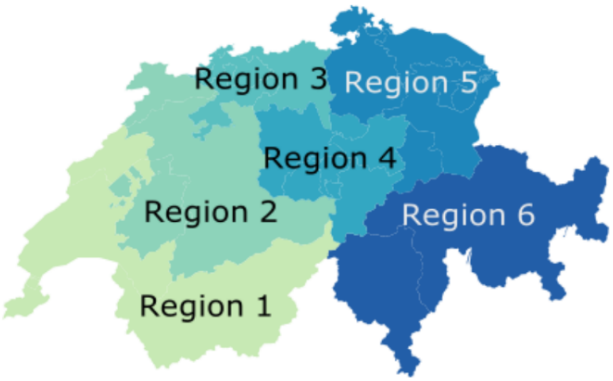
Notably, there has been a substantial and worrying increase in Europe and the rest of the world in mutations leading to escape from Cilgavimab (particularly at position 346). In September, these variants with resistant mutations to both Cilgavimab and Tixagevimab represented over 14% of the sequences identified in Switzerland. For the weeks 38 & 39, this proportion was nearly 18%. Preliminary data for October (2-10 to 21-10, with data available as of 21-10) shows a proportion greater than 30. **The proportion of virus circulating that is completely resistant to Evusheld is rapidly increasing. We expect that all available monoclonal antibodies available in Switzerland will soon be ineffective against the majority of circulating variants.**

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 September (29 August to 2 October), the FOPH reported a total of 81'313 confirmed SARS-CoV-2 cases in Switzerland, representing an increase from August. 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 24'370 positive tests during the surveilled program, which represents about 30% 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 2'506 SARS-CoV-2 sequences have been declared to have been submitted to GISAID during this period. There are 2'450 sequences are available that were collected during this period on GISAID (and 2'657 submitted during this period) as of 26 October 2022, and the difference may be explained by reporting delays and differences between collection/submission dates.

This represents around 3.1% 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
35	Aug. 29 to Sep. 4	583
36	Sep. 5 to Sep. 11	383
37	Sep. 12 to Sep. 18	646
38	Sep. 19 to Sep. 25	396
39	Sep. 26 to Oct. 2	498
	Total	2'506

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 September (weeks 35-39), while the fraction sequenced was generally stable as well. 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.

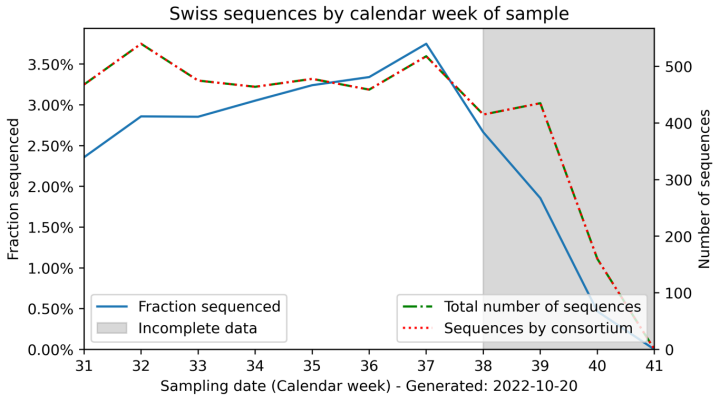


Figure 1: Number of SARS-CoV-2 sequences available for Switzerland (total available Swiss sequences in GISAID in green, Swiss sequences submitted through the program in dotted orange) and fraction of the total number of positive cases declared to the FOPH that have been sequenced (blue curve).

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 approximately 3.0% during the month, with the higher percentages in weeks 36 and 37. 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 region 4 had the lowest fraction of cases sequenced.

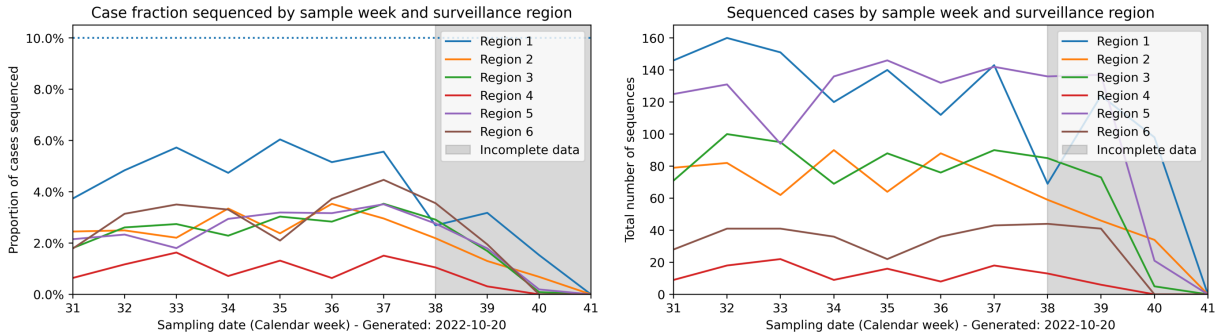


Figure 2: Sequencing coverage among the different Swiss regions per week, presented by fraction of cases sequenced (left) and by number of sequences (right).

4. Recently circulating variants in Switzerland as of August 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 September (Figures 3-5, Table 3). Delta was not detected in Switzerland in September, while Omicron BA.1 was detected just once. 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, 8 BA.2.75 sequences were found in Switzerland in the month of September, a decrease from August. In contrast, 37 BQ.1 sequences were detected, illustrating that BA.5 sublineages are outcompeting BA.2.75 in Switzerland

Region	BA.2*	BA.2.75*	BA.4*	BA.5*	BQ.1*	other	sequences	cases	% sequenced
All	31	8	90	1'906	37	233	2'305	81'313	2.83
1	7	1	24	483	18	55	588	13'524	4.35
2	7	1	19	271	3	30	331	13'917	2.38
3	2	1	15	334	2	58	412	15'361	2.68
4	0	0	2	52	0	7	61	6'834	0.893
5	14	5	21	581	10	62	693	25'357	2.73
6	1	0	6	156	2	21	186	6'320	2.94

Table 3: number of sequences corresponding to selected variants in each region of Switzerland from 29 August 2022 to 2 October 2022, according to data received by 21 October, 2022.

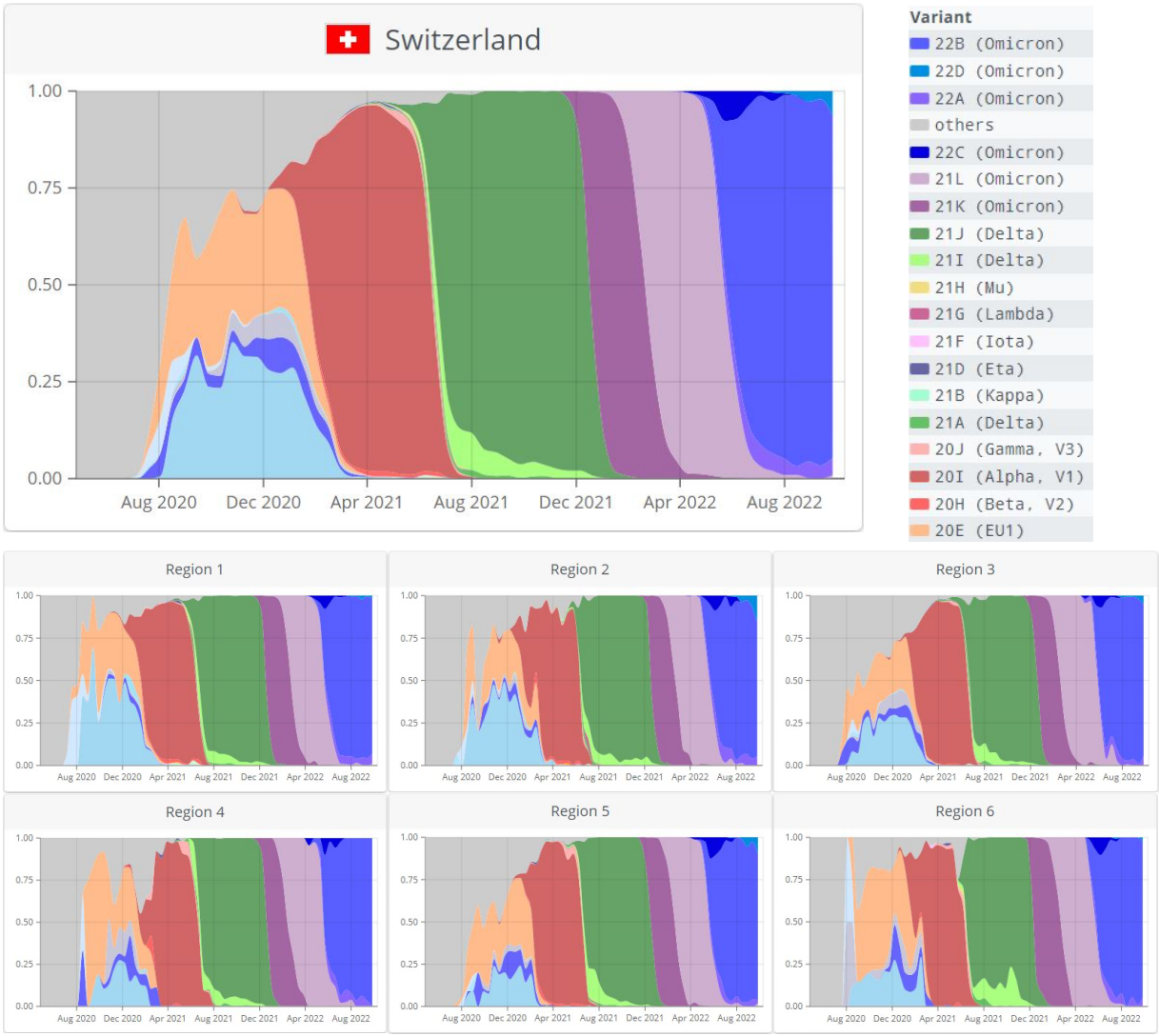


Figure 3: proportion of the total number of sequences (not cases), over time, that fall into defined variant groups, for Switzerland. Screenshot from CoVariants website. Dynamic navigation is available at https://covariants.org/per-country. Dark green indicates the B.1.617.2 (Delta) lineage or its sub-lineages. Dark Red indicates B.1.1.7 (Alpha). Purple/21K indicates Omicron BA.1, Light purple/21L indicates Omicron BA.2. 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. Cyan/22D indicates BA.2.75

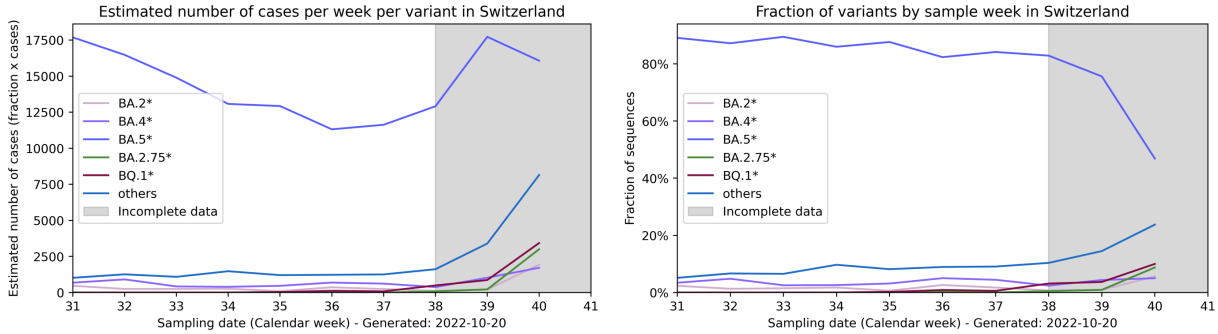


Figure 4: (Left): Percentage of circulating VOCs and VOIs in Switzerland by week, up to the 39 first weeks of 2022 (total number of BA.2, BA.2.75, BA.4, BA.5, and BQ.1 sequences from Switzerland and successfully submitted to GISAID are shown here). Note the grey shaded area indicates a period of incomplete data.
(Right): Estimated number of sequences BA.2, BA.2.75, BA.4, BA.5, and BQ.1 retrieved during the surveilled period.

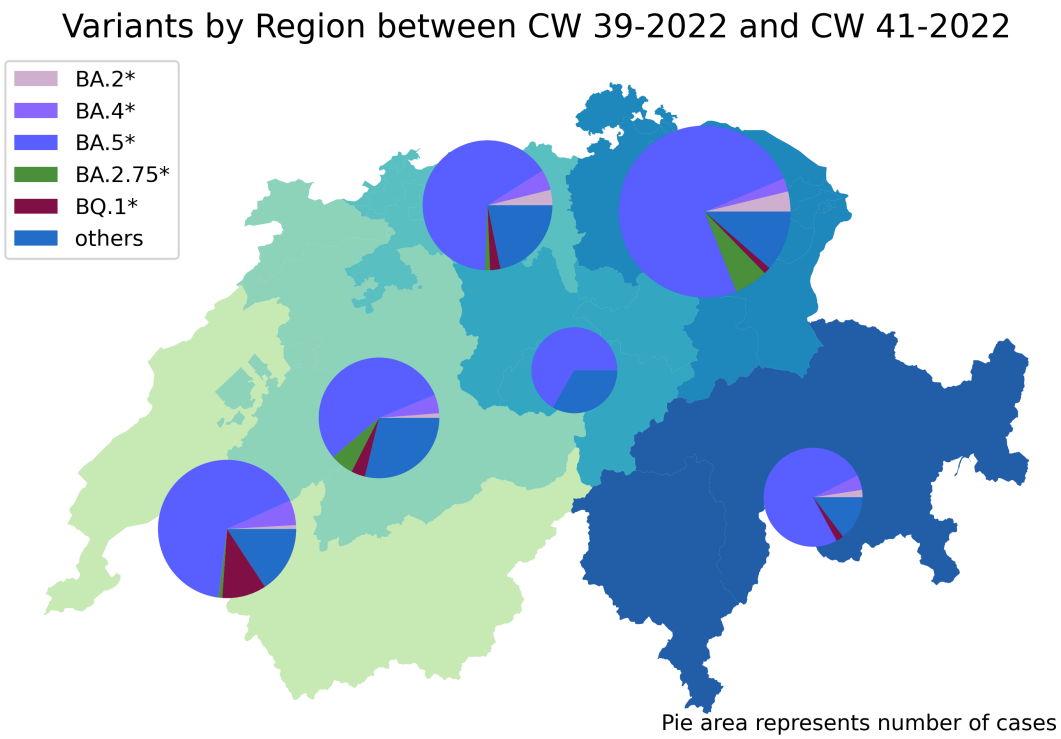


Figure 5: Distribution of variants per region, for the start of October 2022 shown on a map. The size of the pie chart corresponds to the total number of sequences. Note the large share of the share of the BA.5 lineage, and the significant fraction of BQ.1 sequences or other variants in many regions in all regions as of the time of this report.

5. 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. The current estimates suggest that BA.5 prevalence will decline, with other lineages starting to displace it, although which specific lineage is not clear.

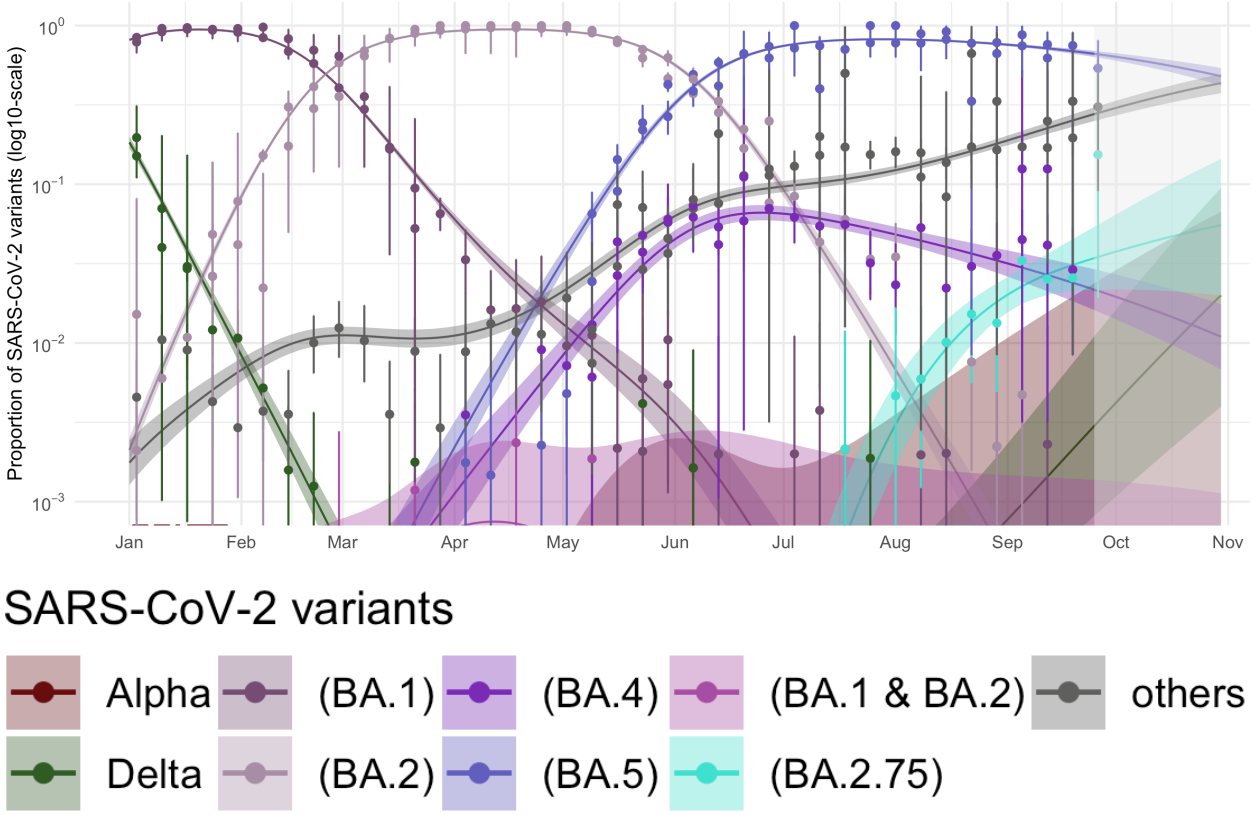


Figure 6: Observed and modeled proportion of SARS-CoV-2 variants over time in Switzerland. Left: graphed by linear proportions. Right: graphed by Log_{10} proportions. Since early 2021, multiple successive variants have been observed to displace all previous variants (often achieving a dominance of >99.9% of the circulation). Alpha was replaced by Delta, followed by Omicron BA.1, then Omicron BA.2, and now Omicron BA.5. Model fits are based on a multinomial logistic regression with splines.

6. 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
29.8 to 2.10	0	0 (Eur: 0)	0	0 (Eur: 0)	0	0 (Eur: 0)	0	0

	340A		340K		340G		340Q	
Dates	Global	Switzerland	Global	Switzerland	Global	Switzerland	Global	Switzerland
29.8 to 2.10	0	0 (Eur: 0)	0.01	0 (Eur: 0.01)	0	0.04 (Eur: 0)	0.01	0 (Eur: 0.01)

	340V		356T		377K	
Dates	Global	Switzerland	Global	Switzerland	Global	Switzerland
29.8 to 2.10	0	0 (Eur: 0)	0.55	0.29 (Eur: 0.46)	0	0 (Eur: 0)

Table 4: Percent (to the nearest 0.01%) of Global and Swiss sequences bearing escape mutations from sotrovimab for September 2022 (29 August to 2 October)

Notably, additional escape mutations against Sotrovimab are currently rare in Switzerland and world-wide. However, the vast majority of circulating variants contain the 371 escape mutations, which are associated with escape >10x) 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.2/4/5, 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, in contrast to the situation with Sotrovimab, known mutations enabling escape from Evusheld® are increasing rapidly in Switzerland and world-wide. During September, variants expected to be completely resistant to Evusheld® (cilgavimab and tixagevimab) made up over 14% of the sequences, and preliminary data for October shows a proportion greater than 30% as of the time of this report. Many of these escape mutations are also associated with 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
29.8 to 2.10	0.96	1.25 (Eur: 1.77)	0.08	0.17 (Eur: 0.13)	0.59	0.21 (Eur: 0.13)	14.62	13.99 (Eur: 14.97)

	444E		444Q		444R		445A	
Dates	Global	Switzerland	Global	Switzerland	Global	Switzerland	Global	Switzerland
29.8 to 2.10	0	0 (Eur: 0)	0.01	0 (Eur: 0.01)	0.83	0.54 (Eur: 0.81)	0.74	0.50 (Eur: 0.61)

	446S		446V		450K		450D	
Dates	Global	Switzerland	Global	Switzerland	Global	Switzerland	Global	Switzerland
29.8 to 2.10	2.57	2.46 (Eur: 1.84)	0.03	0 (Eur: 0.03)	0	0 (Eur: 0)	1.04	1.63 (Eur: 1.24)

Table 5: Percent of Global and Swiss sequences bearing escape cilgavimab mutations for September 2022(29 August to 2 October). 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®. Notably, only 3 mutations have been seen worldwide, resulting in a miniscule percentage of total sequences. Mutations resulting in partial escape from Paxlovid® are shown in table 6.

	144 M/F/A/G/Y		165 T		166 Q/V		167 F	
Dates	Global	Switzerland	Global	Switzerland	Global	Switzerland	Global	Switzerland
29.8 to 2.10	1 (A)	0 (Eur: 0)	0	0	1 (V)	0 (Eur: 0)	0	0

	172 Q/F		192 S/T/V	
Dates	Global	Switzerland	Global	Switzerland
29.8 to 2.10	0	0	1 (T)	0 (Eur: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 September (29 August to 2 October).

7. Wastewater surveillance program

Sequences are obtained from six wastewater treatment plants (WWTPs) that are tested on a daily basis. During the month of September, BA.5 was still by far the most common variant, making up >90% of the sequenced SARS-CoV-2 RNA in all locations (Figures 7, 8). At the end of September, BQ.1.1 accounted for about 3-8% of the sequenced RNA depending on the location.

Considering all data available as of 20 October 2022, BQ.1.1 has been growing in relative abundance at a rate of 0.06-0.08 per day, depending on the location and excluding Altenrhein which appears as an outlier (Figure 9). According to this modelling, the variant is expected to become the major variant sometimes during the first half of November.

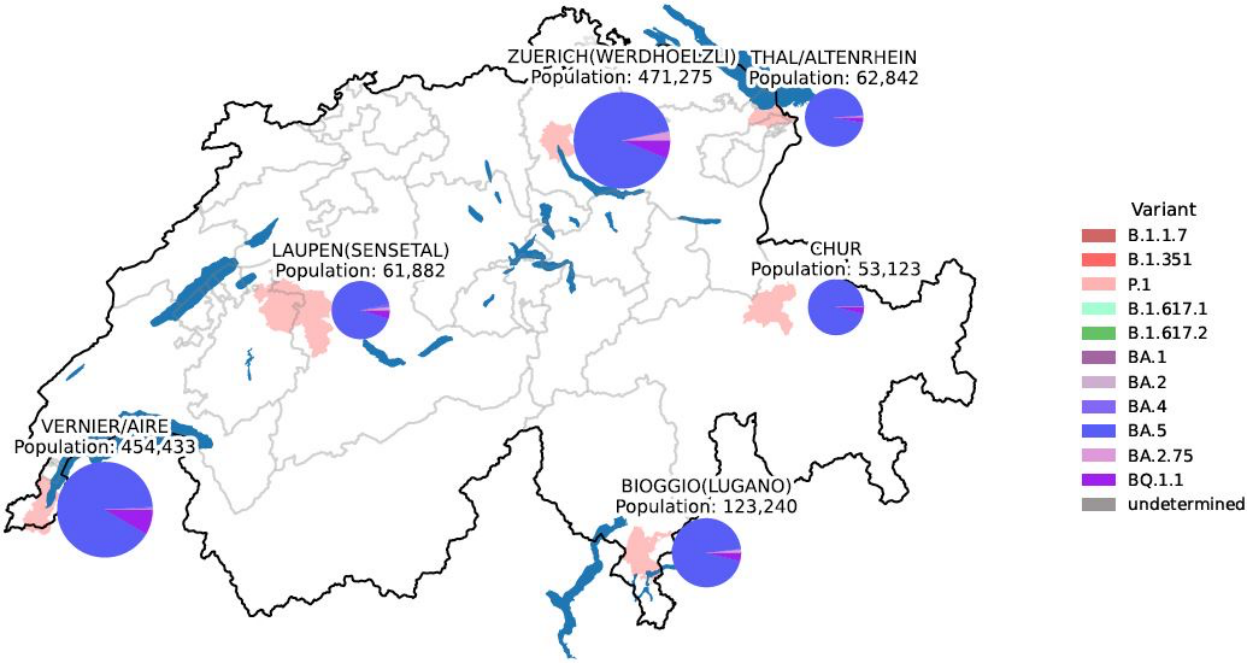


Figure 7:
Overview of the relative abundances of variants of SARS-CoV-2 at the end of September 2022, estimated from wastewater samples collected daily during the month in WWTPs located in 6 different Swiss locations. Pie chart areas are proportional to population connected to the wastewater treatment 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.

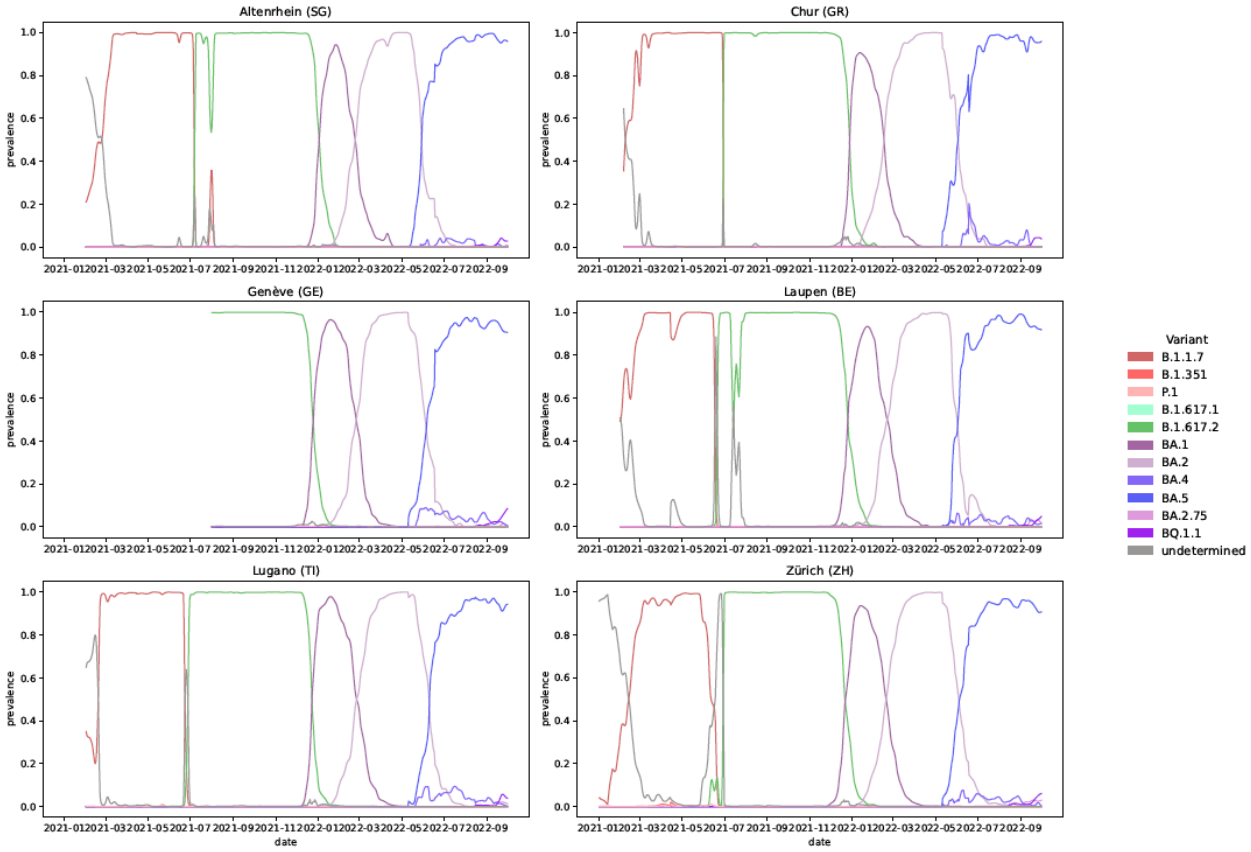


Figure 8: Relative abundances of variants of SARS- CoV-2 estimated from wastewater samples collected daily until September 3, 2022 (except Lausanne: July 31, 2021) in WWTPs located in 6 different Swiss cantons. An online dynamic navigation is available at https://bsse.ethz.ch/cbg/research/computational-virology/sarscov2-variants-wastewater-surveillance.html.

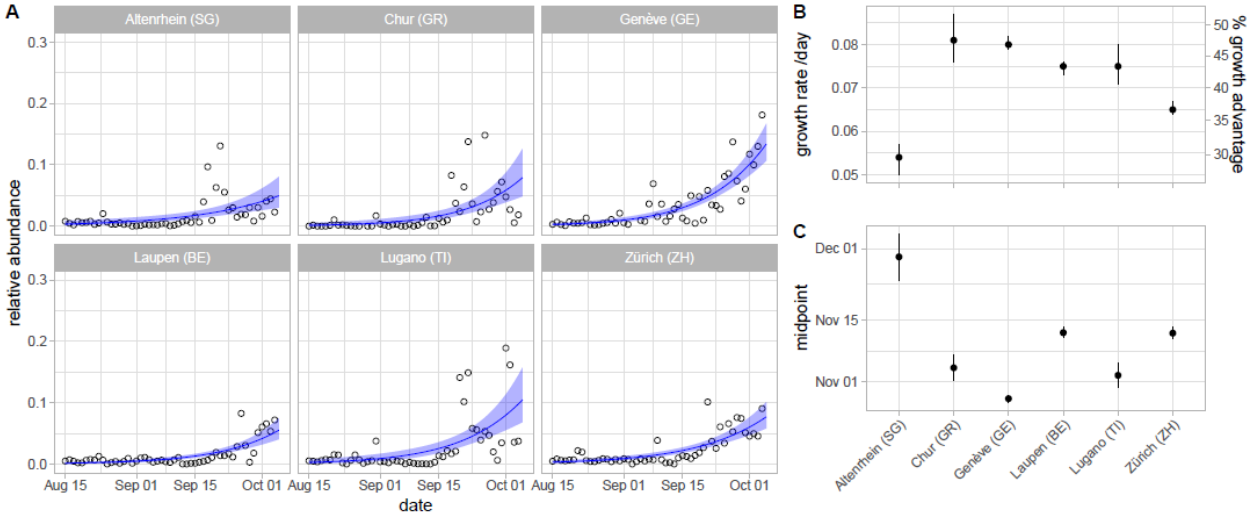


Figure 9: Logistic growth of BQ.1.1 since August 15 in the surveyed wastewater treatment plants. A: fitted curves to the daily estimates of the variant prevalences. B: point estimates and 95% confidence intervals of the logistic growth parameters. Growth advantage is assuming a discrete-time growth model, with generation time of 4.8 days. C: point estimates and 95% confidence intervals of the midpoint parameters.

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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 1 August to 28 August 2022.

sup_table_overview_Sep.xlsx

Supplementary Table 1: Epidemiological data for Switzerland, its regions and cantons for August: 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
35	Aug. 29 to Sep. 4	14 952	4 697	583	31.41%	12.41%
36	Sep. 5 to Sep. 11	14 482	4 384	383	30.27%	8.74%
37	Sep. 12 to Sep. 18	15 252	4 174	646	27.37%	15.48%
38	Sep. 19 to Sep. 25	15 560	4 400	396	28.28%	9.00%
39	Sep. 26 to Oct. 2	18 810	6 715	498	35.70%	7.42%
	Total	79 056	24 370	2 506	30.83%	10.28%

Supplementary Table 2: Total number of tests performed by the laboratories participating in the surveillance program from 29 August to 2 October 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
35	Aug. 29 to Sep. 4	12	19	63	10	40	77	42	38	91	43	107	83	583
36	Sep. 5 to Sep. 11	23	19	66	12	40			36	68			77	383
37	Sep. 12 to Sep. 18	27	25	65	14	40	71	45	34	88	41	140	101	646
38	Sep. 19 to Sep. 25	23	24	50	12	40			44	89			69	396
39	Sep. 26 to Oct. 2	13	23	40	15	40	77	0	37	72	44	63	74	498
	Total	98	110	284	63	200	225	87	189	408	128	310	404	2506

*Supplementary Table 3: number of sequences submitted to GISAID by each laboratory during the surveilled period (29 August to 2 October 2022). *including sequencing sent to high-throughput platforms.*

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