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

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1. Summary

In April, COVID-19 cases numbers gradually declined in Switzerland, with the vast majority of cases caused by the BA.2 Omicron variant.

In the midst of this increase in case numbers, approximately 1.7% of the total number of cases identified in Switzerland in April were sequenced by the Surveillance program, yielding over 1,900 sequences.

Delta circulation has effectively stopped in Switzerland, with only 1 sequence detected in April. The circulation of BA.1 and its subvariants was extremely low in April, with only 32 sequences detected.

The new sub-variant BA.2.12.1, which is poised to become the dominant variant in the USA, was detected only twice in Switzerland during the month of April. Similarly the BA.4 and BA.5, which have achieved dominance have been detected in South Africa, were detected only 4 times in Switzerland during the month of April.

BA.2.12.1 is a subvariant of BA.2, with the notable addition of a mutation at position 452 of its spike protein's binding domain. BA.4 and BA.5 are identical in their Spike protein, which closely resembles the Spike of BA.2, with a few additional mutations, including a mutation at position 452 of its spike protein's binding domain.

Because these new variants sequences are much closer to BA.2 than BA.1, the explosive growth seen by BA.4/5 in South Africa and BA.2.12.1 in the USA (whose previous waves were largely driven by the BA.1 variant) may not be applicable in Switzerland (whose most recent wave was largely driven by BA.2).

Notably however, the BA.4/5 variants bring with them resistance to the antibody therapies of Evushield and Sotrovimab. The data for BA.2.12.1 is currently unclear with regard to Evushield.

Recently, reports of paediatric hepatitis in multiple countries have been reported. At this moment, it is plausible that a connection to SARS-CoV-2 exists. If true, the timing may suggest a variant specific effect, highlighting the continued value of genomic surveillance.

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

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

This report has been produced by 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, Nadja Wipf, Michael Bel, 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 April 4 to May 1, 2022 (weeks 14, 15, 16, 17). All data presented in this report are based on the sampling date. March 2022 was the last month covered under the original national surveillance program funding. The program has been continued at a lower funding level, so there will be less data for this month's report, and for subsequence reports.

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---22-march-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). These mutations are associated with both immune escape and/or increased transmissibility, conferring this variant a growth advantage. It has split into 5 sublineages: BA.1-5. All BA.X sublineages share most Spike RBD mutations, but significant differences are seen in the N-terminus (affecting antibody recognition).

By week 9 (28-February to 6-March 2022) BA.2 was dominant in Switzerland. BA.4 and 5 were first detected in South Africa at the start of April, and rapidly displaced BA.2 there. 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 RBD, which is also found in Delta, and has been associated with both increased ACEII affinity and decreased neutralization by mAbs/poly-clonal sera.

A new BA.2 sublineage, BA.2.12.1, with an L452Q (as opposed to R, which is found in BA.4/5 and Delta) has been detected, and is achieving dominance in the USA.

At the moment it is clear that BA.4/5 and BA.2.12.1 will outcompete BA.2, but it is unclear how they will fare against each other. Notably BA.2.12.1 is much more similar to BA.2 than BA.4/5 are, and BA.4/5 as well as BA.2.12.1 are more antigenically similar to BA.2 than the BA.1. This may lead to different outcomes depending on if a region had a strong BA.1 wave or not before BA.2 became dominant, due to population level immunity from previous exposures.

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 absence is soon expected to be indicative of a BA-4/5 infection rather than a BA.1 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 now demonstrates that Omicron variants are able to evade neutralizing antibodies (nAbs) raised against previous variants or after 2 doses of vaccine. Notably, all Omicron sublineages display complete escape from combination of casirivimab/imdevimab (REGN-CoV2), one of the monoclonal antibody treatments available in Switzerland. Sotrovimab is currently the only antibody available in Switzerland that retains substantial neutralizing activity against BA.1. According to *in vitro* data, BA.2,4 and 5 are significantly more resistant than BA.1 and ancestral variants to Sotrovimab. 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

In vitro studies using live virus show severe reductions to the IC_{90} titer against BA.2, and a recent study failed to find any beneficial effect of Sotrovimab treatment in the context of BA.2 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 Omicron. In the community setting, this moderately effective humoral response after a 3rd dose and the retained cellular response translates to moderate (>50%) vaccine effectiveness against symptomatic infection, high effectiveness against severe outcomes, and very high efficacy at preventing hospitalization and death. Even after 3 doses, immunity will begin to wane. Four doses have been shown to be highly effective at preventing hospitalization and death. 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%.

Despite both being considered "Omicron", BA.1 and BA.2 differ from each other (in terms of mutation counts) more than the earlier VOCs differed from the original Wu-1 strain, which raised concerns about cross protection. Studies have found that infection with BA.1 generally offers cross-protection against BA.2, and vice versa, with only a low rate of reinfection with BA.2 following a BA.1 infection. Similarly, some subjects are known to have failed to develop neutralizing antibodies against BA.2 after BA.1 infection. As BA.4/5 are even more divergent from BA.1, at this moment it is unclear to what extent a prior infection with BA.1 will protect against infection by BA.4/5. The spike in cases in South Africa suggests a significant proportion of the population is susceptible to BA.4/5, but it is unclear if these results are applicable to the Swiss population. Notably, the Omicron wave in South Africa was primarily driven by BA.1, in contrast to the Omicron wave in Switzerland had a higher proportion of BA.2 cases.

Severity

A multitude of clinical, *in vitro* and *in vivo* studies indicate that Omicron BA.1 and BA.2 cause intrinsically milder disease. 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. A recent study attempting to adjust for confounding factors challenged this perception, and found the odds ratios for severe disease were not significantly changed after correcting for other factors.

Despite this argument over intrinsic severity, it is clear that the reality of the current situation is that the odds of severe disease are now much lower. There is currently no good reason to expect that the few additional mutations in BA.4 and BA.5 will substantially alter this.

The Delta VOC

Delta has become extremely rare in Switzerland, with only 1 case detected in April. It is unlikely to continue to be a factor in the epidemic, barring the emergence of a new sub-lineage from an as yet undetected source (chronic infection, animal reservoir, etc.).

Recombinants

Recombinant virus formation occurs by coinfection by 2 different strains within the same host. Numerous verified recombinants between Delta and Omicron BA.1 have been detected, as well as between different Omicron sublineages. Some of those recombinants include those with the Pango lineage designations: XD, XE and XF. So far there has been no sign of significant growth of any of these recombinants.

Therapeutic intervention effectiveness

Numerous mutations have been reported to substantially reduce the therapeutic effectiveness of mAbs currently used to treat COVID-19, as well as those under development (Table 1). Notably, BA.2 substantially escapes neutralization by Sotrovimab. Evusheld, a combination of tixagevimab and cilgavimab, will also be used in Switzerland. Tixagevimab is not effective against BA.2, but cilgavimab is expected to retain efficacy against BA.2. Cilgavimab is known to have reduced neutralizing capacity against BA.4/5, and reports about neutralizing capacity against BA.2.12.1 are mixed. As Sotrovimab is still being used and Cilgavimab will be used, additional mutations causing escape from them will thus be closely followed (Table 1, and section 7).

AA position	World	Europe	Switzerland	Mutations
Sotrovimab				
337	19	13	0	R/L/H/T
340	177	122	7	K/A/G/Q/V
356	91	61	0	T
377	0	0	0	K
Cilgavimab				
346	9	4	0	I
371	334 542	198 059	1 686	F
444	81	48	1	R/Q/E
445	38	25	0	A
446	11409	4239	16	S/V
450	2	2	0	K
452	2 739	1 163	7	R

Table 1: Positions where mutations are known to result in escape from sotrovimab or cilgavimab, their prevalence, and the specific amino acid mutations known to result in escape, April 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.

In addition to mAbs, there are a number of other antiviral treatments under development, such as 3CL like protease inhibitors like Paxlovid® (PF-07321332) or RNA nucleotide analogues (which interfere with replication of the viral genome, such as Molnupiravir). No data is available regarding mutations enabling escape from these proteases. In contrast, serial passage of virus in the presence of Molnupiravir led to resistance at the cost of significantly reduced overall viral fitness. As such mutations are detrimental when Molnupiravir is not present, limited use is unlikely to lead to resistant strains. Preliminary data confirms that Molnupiravir, Paxlovid, and Remdesivir all retain full *in vitro* efficacy again Omicron.

There have been numerous reports of viral titers rebounding, accompanied by a return of symptoms, following a 5-day course of Paxlovid. Notably, this means that Paxlovid was effective, successfully lowering viral loads and reducing symptoms, during the treatment. There is currently no indication of any variant specific rebound effects, or loss in treatment efficacy.

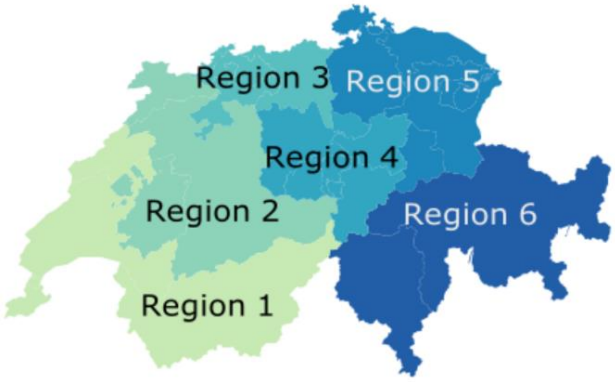
The circulation of specific mutations leading to decreased effectiveness of known therapeutics available for clinical use in Switzerland will be surveilled (see Section 7), but their prevalence remains low.

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 April, the FOPH reported a total of 111,040 confirmed SARS-CoV-2 cases in Switzerland, representing a substantial decrease from March. 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 42,302 positive tests during the surveilled program, which represents about 38% of the total number of cases reported in Switzerland (including both PCR and antigen-based tests). 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 1,929 SARS-CoV-2 sequences have been declared to have been submitted to GISAID during this period. There are 1,853 sequences are available for this period on GISAID as of 24 May 2022, and the difference may be explained by reporting delays.

This represents around 1.7% 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
14	Apr 4 to Apr 10	502
15	Apr 11 to Apr 17	637
16	Apr 18 to Apr 24	311
17	Apr 25 to May 1	479
	Total	1 929

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

The total number of SARS-CoV-2 sequences declared and submitted to GISAID by each laboratory during 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 declined during April (weeks 14-17), while fraction sequenced increased, reflecting the decrease 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.

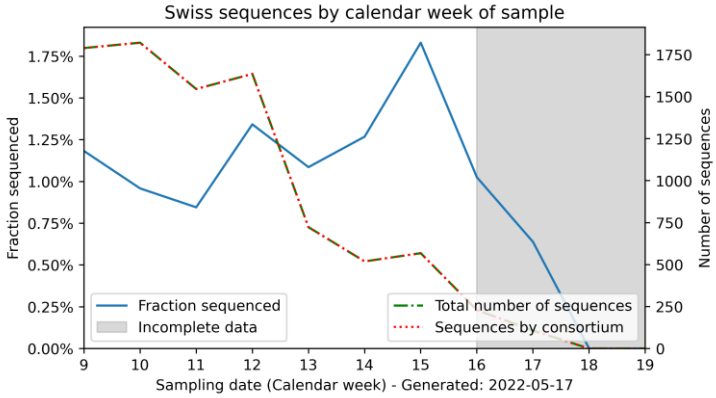


Figure 1: Number of SARS-CoV-2 sequences available for Switzerland (total available Swiss sequences in GISAID in green, Swiss sequences submitted through the program in dotted orange) and fraction of the total number of positive cases declared to the FOPH that have been sequenced (blue curve).

During the surveilled period, the absolute number of sequences generated remained fairly high, at hundreds of sequences per week, but the total proportion of positive sequenced cases was below 2%. 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 continued to have the lowest total number of sequences, and also had the lowest fraction of cases sequenced.

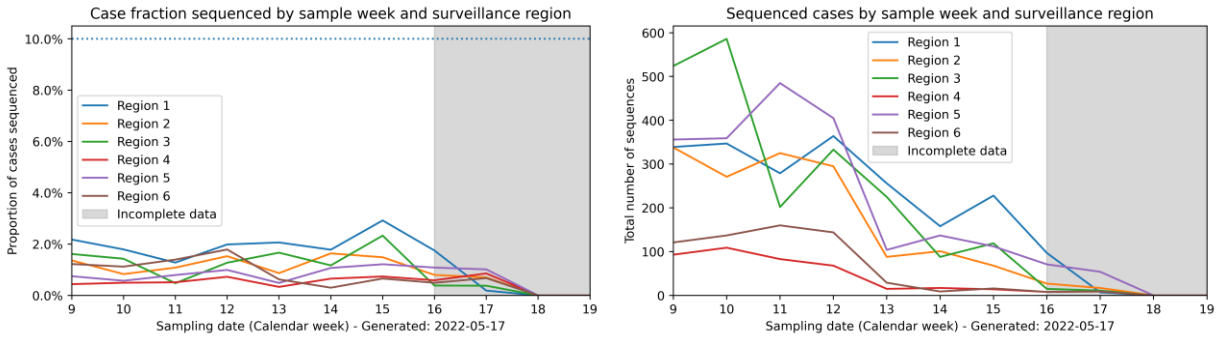


Figure 2: Sequencing coverage among the different Swiss regions per week, presented by fraction of cases sequenced (left) and by number of sequences (right).

5. Recently circulating variants in Switzerland as of April 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.2 was by far the most commonly retrieved lineage in April (Figures 3-5, Table 3).

Region	BA.1	BA.2	BA.2.12.1	BA.4	BA.5	Delta	None	other	sequences	cases	% sequenced
All	32	1357	2	3	1	1	26	1	1423	111040	1.28%
1	10	472	0	0	1	0	6	1	490	25940	1.89%
2	5	204	0	1	0	0	3	0	213	16541	1.29%
3	10	214	0	0	0	0	9	0	233	19420	1.20%
4	1	44	0	0	0	0	3	0	48	6905	0.70%
5	6	362	2	2	0	1	1	0	374	33857	1.10%
6	0	38	0	0	0	0	4	0	42	8377	0.50

Table 3: number of sequences corresponding to selected variants in each region of Switzerland from 4 April 2022 to 1 May 2022, according to data received by 20 May, 2022. Sequences with poor coverage where lineages could not be assigned are excluded.

No BA.3 was found during the surveilled period. During the surveilled period, 3 BA.4 sequences, 1 BA.5 sequence, and 1 XE (BA.1 & BA.2 recombinant) sequence were found in Switzerland. An estimate of the total number of VOCs circulating in Switzerland, corrected by taking in account the fraction of sequencing in Switzerland is available through the covSPECTRUM program, developed at ETHZ, at https://cov-spectrum.ethz.ch/explore/Switzerland.

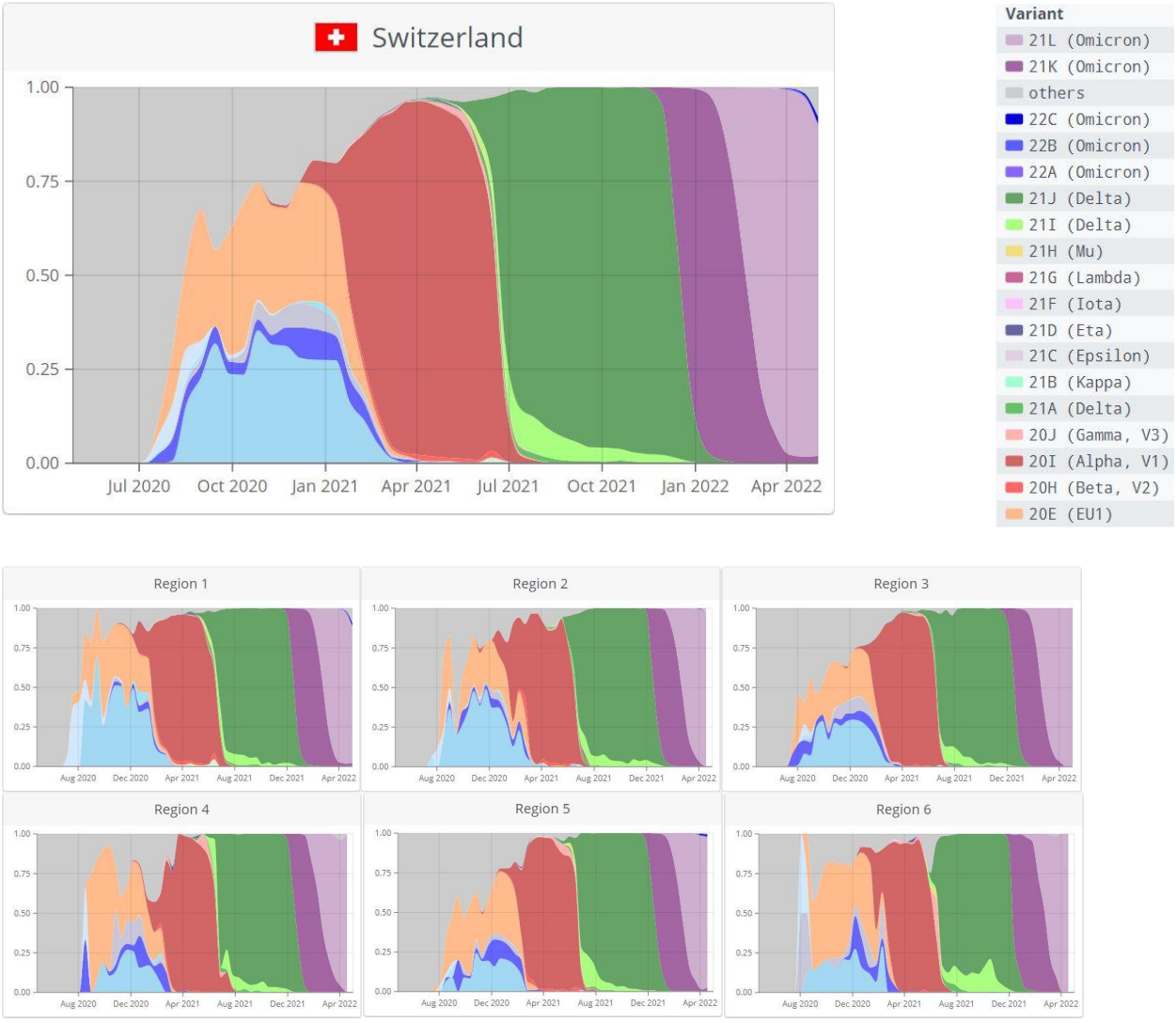


Figure 4: proportion of the total number of sequences (not cases), over time, that fall into defined variant groups, for Switzerland. Screenshot from CoVariants website. Dynamic navigation is available at https://covariants.org/per-country. Dark green indicates the B.1.617.2 (Delta) lineage or its sub-lineages.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

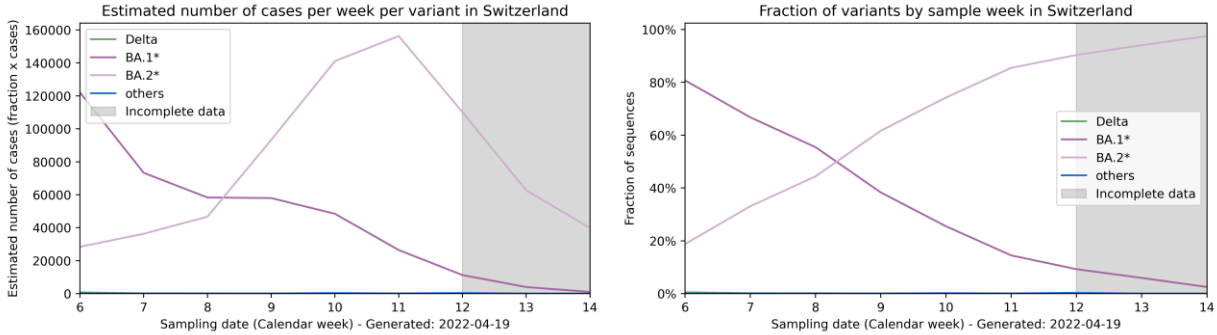


Figure 5: (Left): Percentage of circulating VOCs and VOIs in Switzerland by week, up to the 17 first weeks of 2022 (total number of B.1.617.2 (Delta), BA.1 and BA.2 sequences from Switzerland and successfully submitted to GISAID are shown here). Note the grey shaded area indicates a period of incomplete data.
(Right): Estimated number of sequences of Delta, BA.1, BA.2, and others retrieved during the surveilled period.

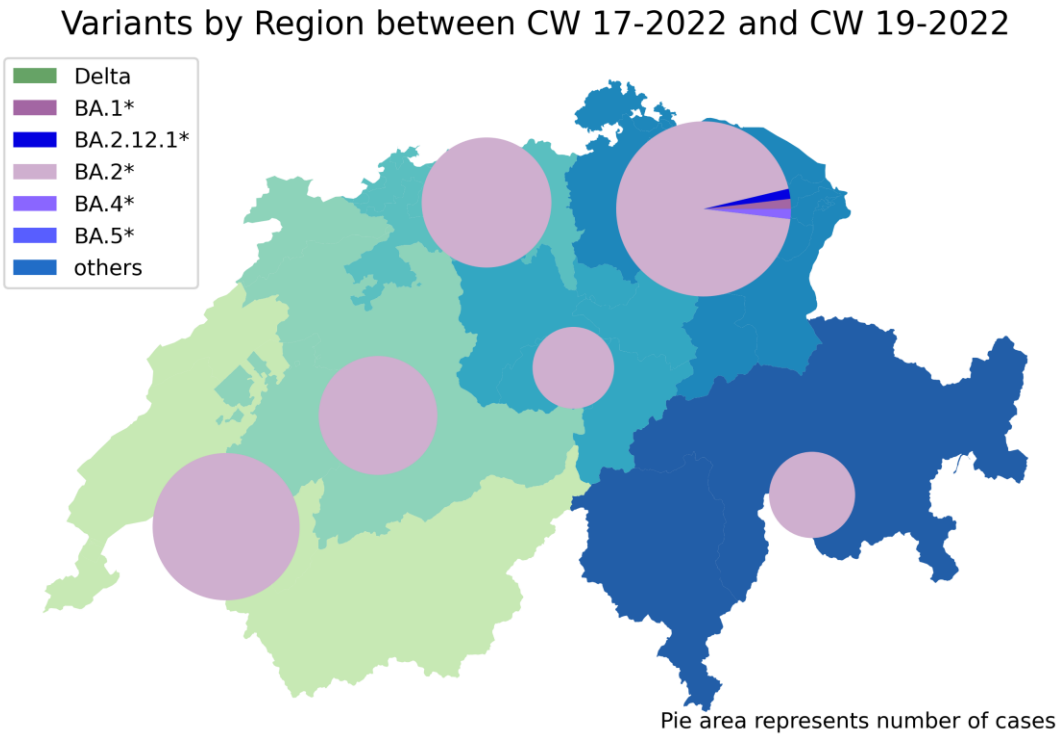


Figure 6: Distribution of variants per region, for the end of April 2022 shown on a map. The size of the pie chart corresponds to the total number of sequences. Note Omicron's extreme dominance, and the large share of the BA.2 sublineage, in all regions as of the time of this report.

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 7).

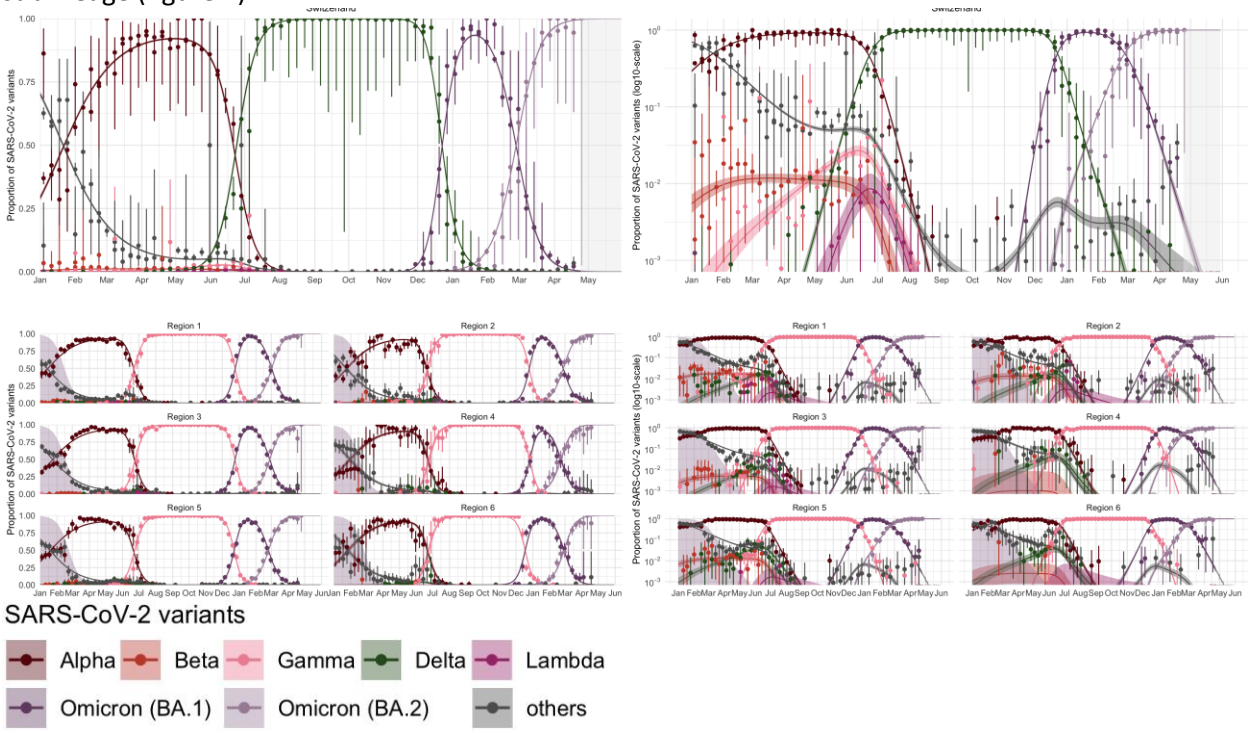


Figure 7: Observed and modeled proportion of SARS-CoV-2 variants over time in Switzerland. Left: graphed by linear proportions. Right: graphed by Log_{10} proportions. In April and May 2021, Gamma and Delta started to replace Alpha, with Delta outcompeting all other variants. At the end of October, more than 99.9% of the retrieved sequences in Switzerland were due to Delta or one of its sub-lineages. In late November, BA.1 arrived in Switzerland and began to rapidly displace Delta. Omicron BA.1 achieved dominance by the end of December, but was then replaced by Omicron BA.2. Data in Switzerland is insufficient for analysis of BA.4/5 or BA.2.12.1 at this time. 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 the BA.2 sublineage (which has replaced BA.1), on the basis of various disparate experiments reporting 8.5 to 340 fold 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
4.4. to 1.5	3	0	4	0	9	0	3	0

	340A		340K		340G		340Q	
Dates	Global	Switzerland	Global	Switzerland	Global	Switzerland	Global	Switzerland
4.4. to 1.5	26	0	114	3	0	0	35	4

	340V		356T		377K	
Dates	Global	Switzerland	Global	Switzerland	Global	Switzerland
4.4. to 1.5	2	0	91	0	0	0

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

As seen in table 4, additional known mutations enabling escape from Sotrovimab have been detected in Switzerland, but remain rare. Notably, 3 patients with escape mutations at position 340 (1x 340 K, 2x 340Q) originate from Geneva. All 3 had been treated with Sotrovimab, suggesting that these mutations emerged in response to Sotrovimab treatment.

Evusheld, which consists of tixagevimab and cilgavimab, will also be 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. One patient with from Geneva had an escape mutation (444R), but has no record of treatment with Evusheld.

	346I		371F*		444R		444Q	
Dates	Global	Switzerland	Global	Switzerland	Global	Switzerland	Global	Switzerland
4.4. to 1.5	9	0	334,542	1686	78	1	0	0

	444E		445A		446S**		446V	
Dates	Global	Switzerland	Global	Switzerland	Global	Switzerland	Global	Switzerland
4.4. to 1.5	3	0	38	0	11404	16	5	0

	450K		452R***	
Dates	Global	Switzerland	Global	Switzerland
4.4. to 1.5	2	0	2739	7

*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.*

8. Wastewater surveillance program

Sequences are obtained from six wastewater treatment plants (WWTPs) that are tested on a daily basis. Signatures of the BA.1 (Omicron) variant were first detected at the earliest in sequenced sewage samples of the Basel-Stadt cantonal wastewater surveillance project, dating from November 21 onwards. Since then, Omicron has been detected in all other surveyed WWTPs, and quickly grew in relative prevalence during the month of December to become the major variant in wastewater samples in most of the surveyed locations by the end of the year, and in all surveyed locations by the beginning of January. Since the end of January, BA.2 has been steadily increasing in all wastewater treatment plants of the program. By the end of the month of February, the BA.2 variant was dominating in all surveyed areas. By the end of March, BA.1 had almost completely disappeared, having been replaced by replaced by BA.2.

Quantification of Omicron in sewage has exhibited some peculiar challenges (in Switzerland and in other countries): some data indicates that this variant is less shed in faeces compared to Delta. The differential shedding could lead to an underestimation of the prevalence of Omicron relative to Delta when using wastewater sequencing data. This bias is not expected at the moment to impact quantification of BA.2 relative to BA.1. Other challenges in the quantification of variants from wastewater sequencing data stem from shared mutations between lineages, which can under some conditions lead to inferring spurious low frequency prevalence of some variants, and our methodology is evolving to mitigate these effects.

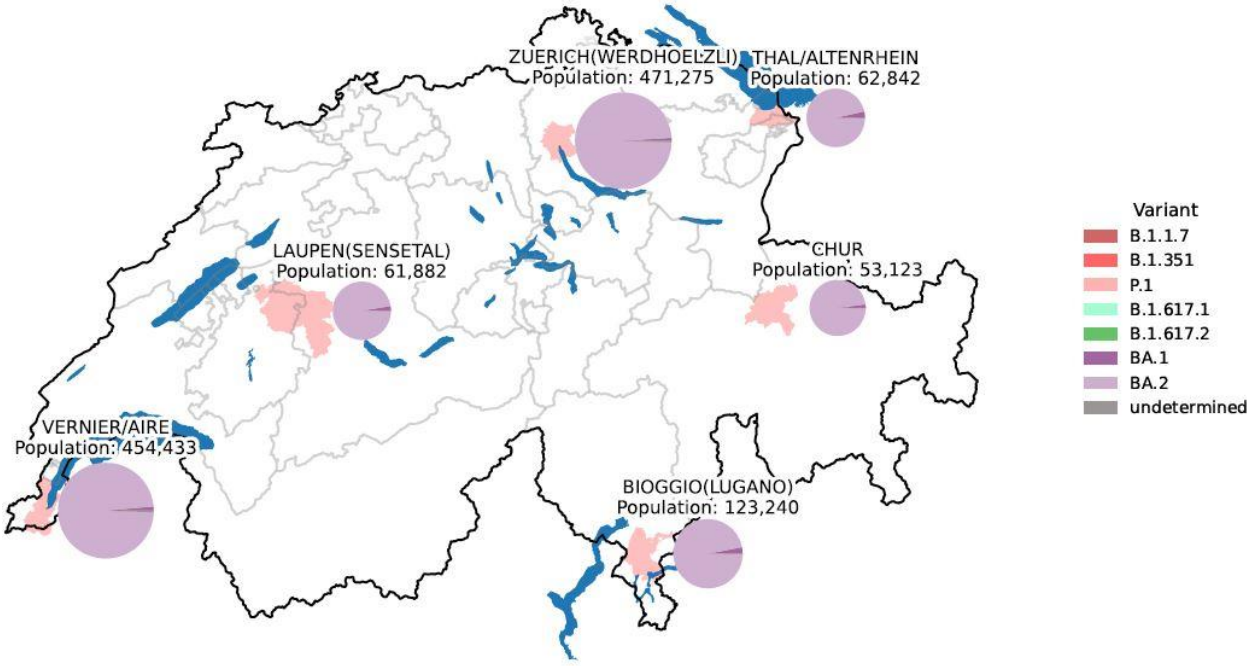


Figure 8:
Overview of the prevalence of variants of SARS-CoV-2 at the end of April 2022, estimated from wastewater samples collected daily during the month in WWTPs located in 6 different Swiss locations. Pie chart areas are proportional to population connected to the wastewater treatment plants. Pink 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. B.1.617.2 (Delta) is represented in in dark green, B.1.617.1 in light green (Kappa), B.1.617.3 in purple, B.1.1.7 (Alpha) in dark red, B.1.351 (Beta) in light red, P.1 (Gamma) in pink, BA.1 (Omicron) in dark purple, and BA.2 (Omicron) in light purple.

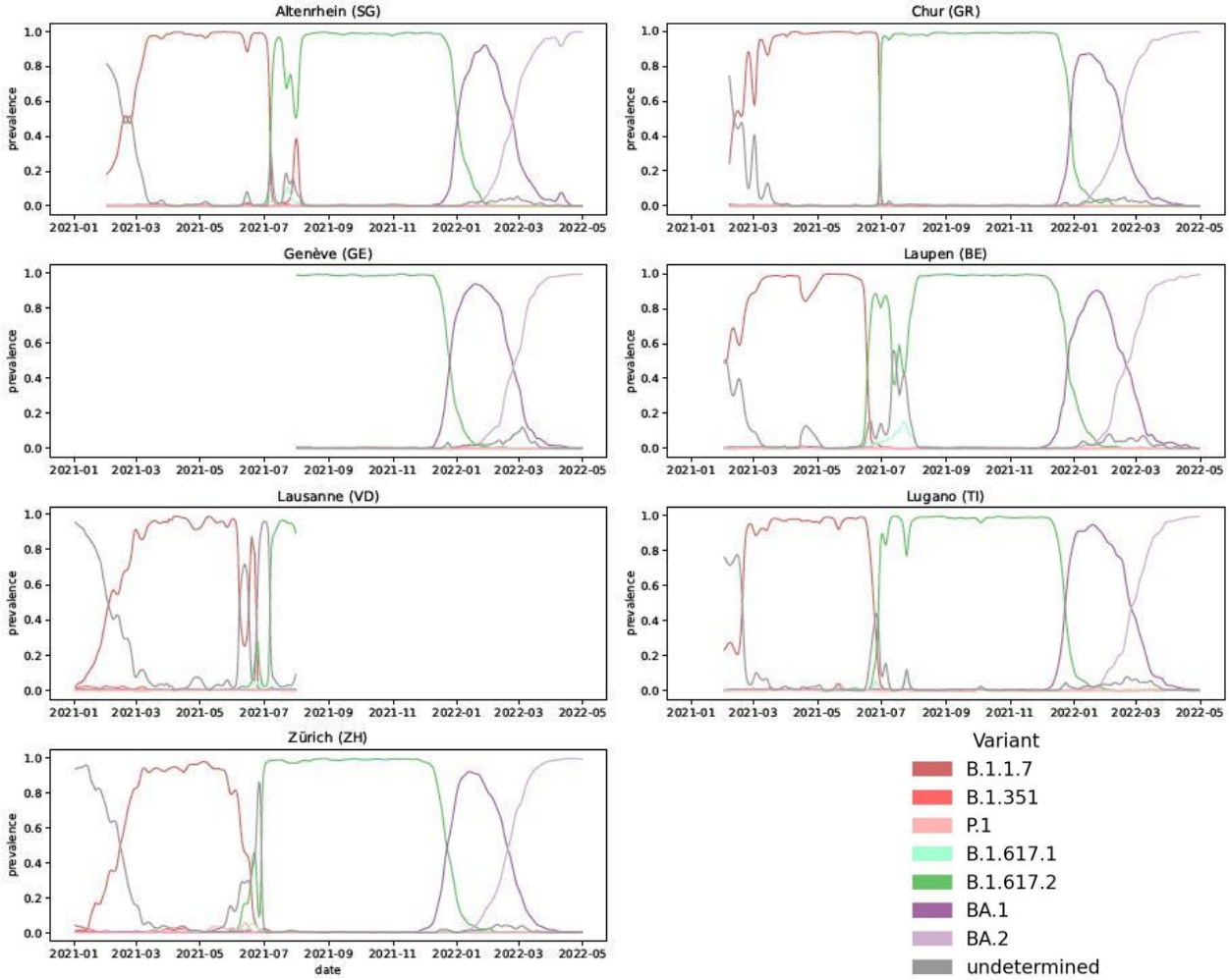


Figure 9: Prevalence of variants of SARS- CoV-2 estimated from wastewater samples collected daily until March 31 (except Lausanne: July 31) in WWTPs located in 7 different Swiss cantons. B.1.617.2 (Delta) is represented in dark green, B.1.617.1 (Kappa), in light green, B.1.617.3 in purple, B.1.1.7 (Alpha)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

Acknowledgements:

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 here cover the period from 4 April 2022 to 1 May 2022.

sup_table_overview_Apr.xlsx

Supplementary Table 1: Epidemiological data for Switzerland, its regions and cantons for April: 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
14	Apr 4 to Apr 10	42 696	15 678	502	36.72%	3.20%
15	Apr 11 to Apr 17	33 082	11 689	637	35.33%	5.45%
16	Apr 18 to Apr 24	26 484	8 662	311	32.71%	3.59%
17	Apr 25 to May 1	22 839	6 273	479	27.47%	7.64%
	Total	125 101	42 302	1 929	33.81%	4.56%

Supplementary Table 2: Total number of tests performed by the laboratories participating in the surveillance program from 4 April 2022 to 1 May 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
14	Apr 4 to Apr 10	0	0	64	15	24	0	20	37	85	20	77	160	502
15	Apr 11 to Apr 17	0	0	58	5	3	37	0	35	78	37	142	242	637
16	Apr 18 to Apr 24	0	0	52	12	45	0	45	41	55	0		61	311
17	Apr 25 to May 1	24	0	59	17	48	77	0	36	60	39	73	46	479
	Total	24	0	233	49	120	114	65	149	278	96	292	509	1 929

*Supplementary Table 3: number of sequences submitted to GISAID by each laboratory during the surveilled period (4 April to 1 May 2022). *including sequencing sent to high-throughput platforms. ND = No data*

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