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Swiss national SARS-CoV-2 genomic and variants surveillance program: report of the month of January 2023

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1. Summary

Since January 1rst, 2023, SARS-COV-2 RT-PCR tests are no longer covered by the Swiss Confederation and reimbursement by health insurance is restricted to vulnerable patients who could benefit from an antiviral treatment. This resulted in a drastic decrease of COVID-19 cases numbers diagnosed in Switzerland. The number of confirmed cases is thus a severe underestimate of the true case numbers. In parallel, the Swiss national SARS-CoV-2 genomic and variants surveillance program has been adapted, and starting in January 2023, sequencing volume supported by the program has been reduced to a maximum of 200 sequences per week, and is now carried out by only 7 centers in one sequencing facility. In Switzerland in January, 500 sequences were sequenced by the Surveillance program, a decrease from the >2,000 of December.

The majority of the sequences in Switzerland belong to the BQ.1 sublineage of BA.5, with the XBB.1.5 variant (a recombinant between two BA.2 sublineages) beginning to overtake it.

XBB.1.5 variant exhibits higher affinity for ACE2, and thus presumably higher transmissibility. In vitro neutralization data does not suggest that it has enhanced immune escape relative to the other variants with significant circulation (such as the recently dominant BQ.1).

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 and it continues to grow. While the bivalent BA.1 booster could 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.

The currently circulating variants are resistant to all the monoclonal antibody therapies used in Switzerland. Sublineages with mutations enabling complete escape from cilgavimab (thus, complete escape from Evusheld®) are now dominant (>95% of circulating viruses). All available monoclonal antibodies available in Switzerland are thus unable to effectively neutralize most circulating SARS-CoV-2 viruses. Despite this, hospitalization rates are down due to previous immunity and protection from previous exposure/vaccination.

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. It began in March 2021 and is currently funded through 2023.

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.

As of the beginning of January, 2023, the program was adapted and restricted to 7 participating laboratories, comprising the University Hospital Centres in Geneva, Lausanne, Bern, Basel, Zurich, and Ticino), in addition to the cantonal hospital in Valais (Hôpital du Valais – Institut Central), and 1 high-throughput sequencing platform (Health 2030 Genome Centre in Geneva). In addition, since the month of October 2022, sequencing in Geneva has been partially funded by the EU grant for the COVICIS project (https://covicis.eu/).

Processed sequencing data are shared openly 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, the program includes sequencing of SARS-CoV-2 in wastewater samples. Samples are collected daily in six wastewater treatment plants (WWTP), under the coordination of Eawag. 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). Since the beginning of January 2023, the surveillance in wastewater in no longer included in the national surveillance program but benefits from another source of funding.

Immunological characterization of the variants within the surveillance program was included until December 2022 and was 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, 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 2 January 2023 to 29 January, 2023 (weeks 1,2,3,4). 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 since the beginning of 2022 (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" and/or have recombined together to form recombinant lineages. 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 the BA.5 sublineage BQ.1 being dominant in most of January, with the XBB.1.5 variant (a recombinant between two BA.2 sublineages) beginning to overtake it (see below).

While BA.5 and its BQ.1 sublineage replaced BA.2 in Switzerland, highly derived BA.2 sublineages have continued to persist and diversify worldwide. Most circulating Omicron subvariants now contain mutations that seem to confer a growth advantage and enable complete escape from cilgavimab, rendering it fully resistant to the combination therapy Evusheld®.

A recombination event between a BA.2.10 sublineage (BJ.1) and a BA.2.75 sublineage (BM.1.1.1) has produced the XBB lineage, which also showed strong signs of growth and immune escape. In particular a sublineage, XBB.1.5 has emerged that is showing signs of overtaking BQ.1 and may be the next dominant variant. Notably, this variant seems to have similar immune escape properties to BQ.1.1, but has a higher ACE2 affinity, presumably enhancing its inherent transmissibility.

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 or BA.2 derived infection. Likewise, its presence is indicative of a likely BA.5 (or BA.5 subvariant, such as BQ.1) 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. There is no evidence that the new subvariants pose any particular detection challenges to these tests.

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 and sublineages thereof by sera from BA.1 and BA.2 vaccine-breakthrough infections. For BA.5, this was shown to lead to decreased protection against hospitalization relative to BA.2 infections, although this difference was reduced after 3 vaccine doses, and it was nearly absent after 4 doses. BA.2.75, BA.4 and BA.5 sublineages containing further escape mutations, in particular BQ.1* and XBB, have been shown to be substantially less neutralized than earlier variants by patient sera, even if the sera comes from people exposed to "basic" BA.2, BA.4 or BA.5 as well as people who have been boosted by Bivalent vaccines. Furthermore, the currently circulating forms of

these sublineages completely escape neutralization by Evusheld® and have substantially reduced neutralization by sotrovimab. 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.

While all Omicron sublineages largely escape humoral immunity from pre-omicron vaccines and infections, cell mediated immunity remains mostly intact. Efficacy preventing hospitalization and death is reduced but remains high after three doses and is even higher after four doses. The efficacy of four doses at preventing symptomatic disease is relatively high (>60%), but remains poor (~30%) at preventing any infection.

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. One large study from Japan seems to confirm that BA.5 did indeed cause more severe disease than BA.2, yet the severity was still lower than pre-Omicron variants.

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. The cause of this attenuation is not clear, but mutations in the NSP6 gene and the E gene have been implicated.

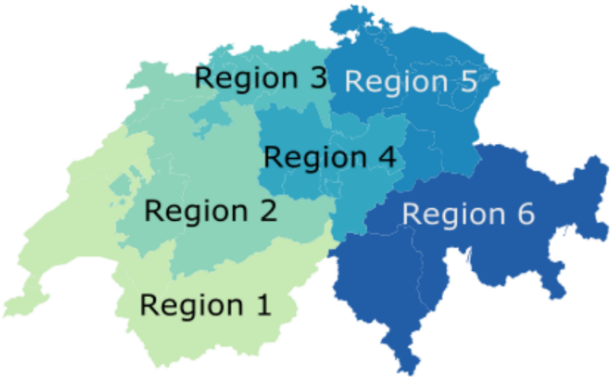
There is currently no evidence that the severity of the new subvariants (such as XBB.1.5 and BQ.1.1,) has significantly changed.

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 January (2 January to 29 January), the FOPH reported a total of 1'898 positive tests (including both RT-PCR and antigen-based tests) were processed by labs participating in the national surveillance program. The number of confirmed positive cases dropped sharply in January, likely due to a change in test reimbursement policy, resulting in a drop in the rate of case ascertainment. Although case ascertainment rates are currently too low to identify meaningful trends, there has not been any sign that the currently low hospitalization rates are rising. 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. 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 2.

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

A total of 507 SARS-CoV-2 sequences have been declared to have been submitted to GISAID during this period. There are 1'652 sequences available that were submitted during this period on GISAID (and 403 collected during this period) as of 27 February 2023. This contrast between the numbers of submitted and collected sequences is likely due to reporting delays, yet the contrast has never been so high. The sharp reduction in sequences collected during this time frame likely indicates a large overall reduction in sequencing starting in January 2023.

Table 1 shows the number of sequences successfully submitted to GISAID through the surveillance program during the surveilled period by calendar week.

Week	Date	Number of sequences declared and successfully submitted to GISAID during the surveilled period, by all laboratories in the program
1	Jan. 2 to Jan. 8	311
2	Jan. 9 to Jan. 15	0
3	Jan. 16 to Jan. 22	196
4	Jan. 23 to Jan. 29	0
	Total	507

Table 1: 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 dropped sharply in January (weeks 1-4) as a result of the reduced scope of the new sequencing program. 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.

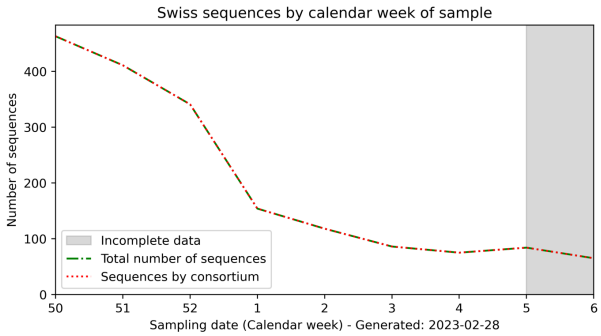


Figure 1: Number of SARS-CoV-2 sequences available for Switzerland (total available Swiss sequences in GISAID in green, Swiss sequences submitted through the program in dotted orange).

During the surveilled period, the absolute number of sequences generated dropped into the hundreds, roughly 4 fold decrease from the previous month.

Figure 2 displays the number of SARS-CoV-2 cases sequenced for each Swiss region. Region 4 continues to have the lowest number of sequences.

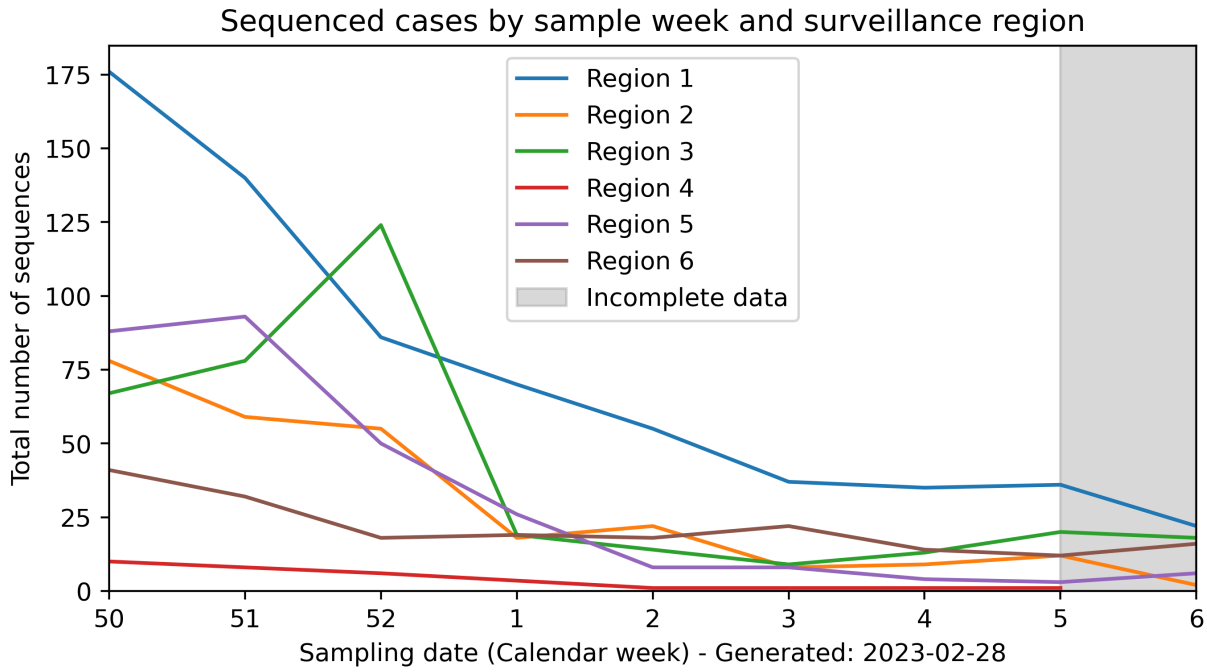


Figure 2: Sequencing coverage among the different Swiss regions per week, bynumber of sequences.

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).

Basal Omicron BA.5 has now been greatly surpassed by its BQ.1 sublineage (Figures 3-5, Table 4) as the most common variant in Switzerland during January (of which BQ.1.1 was the most common). In Switzerland, Delta has not been detected since July 2022 and BA.1 has not been detected since December. 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, 56 BA.2.75 sequences were found in Switzerland in the month of January, a similar amount to that of November. Notably, 37 XBB.1.5 sequences were detected in January.

Region	BA.2*	BA.2.75*	BA.5*	BQ.1*	XBB*	other	sequences
All	3	53	51	259	46	21	433
1	1	25	21	111	27	12	197
2	0	3	11	38	4	1	57
3	1	13	10	27	4	0	55
4	0	0	0	0	1	0	1
5	0	4	5	32	3	2	46
6	1	8	4	49	5	6	73

Table 2: number of sequences corresponding to selected variants in each region of Switzerland from 2 January to 29 January 2023, according to data received by 27 February, 2023.

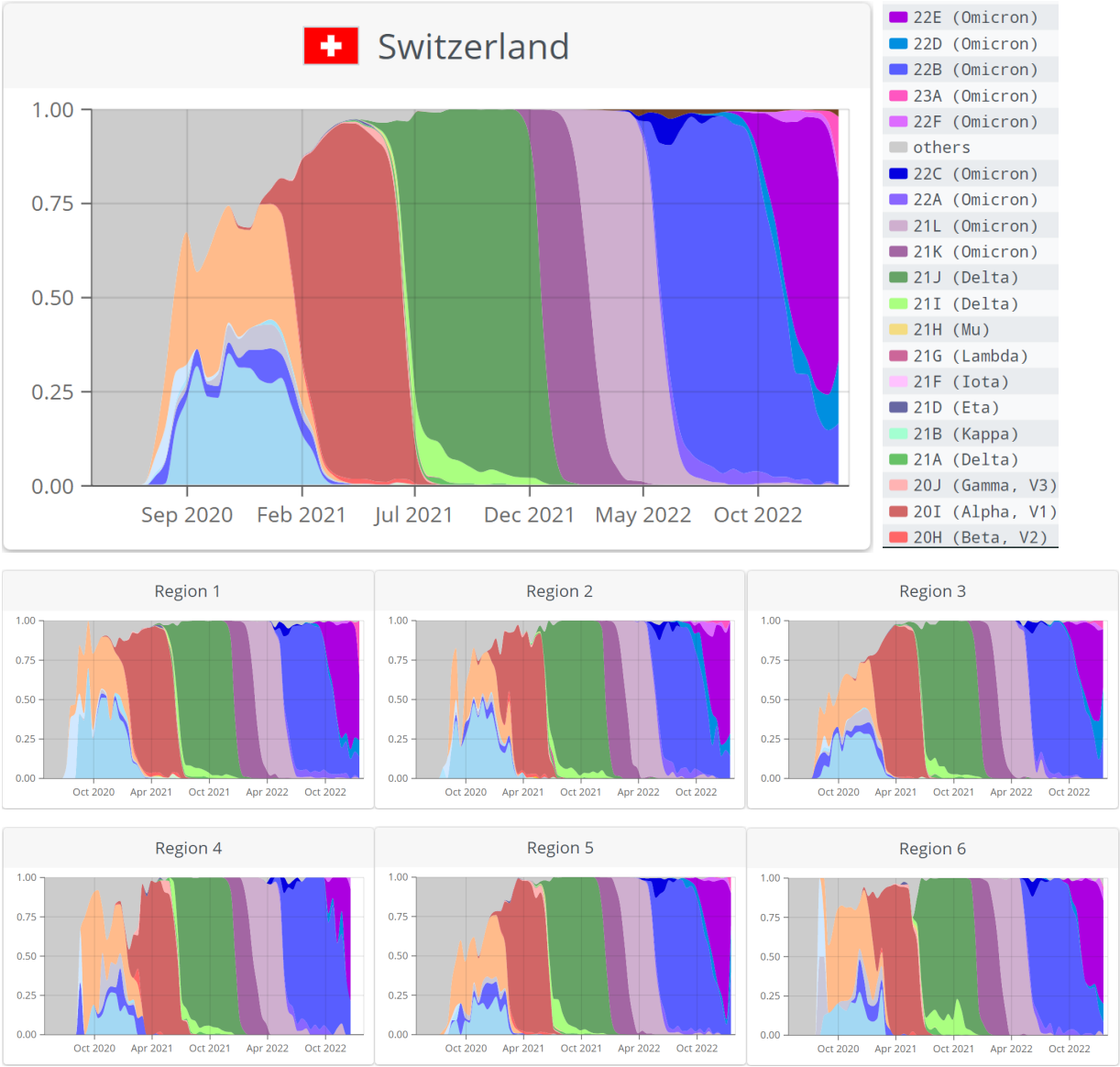


Figure 3: proportion of the total number of sequences (not cases), over time, that fall into defined variant groups, for Switzerland. Screenshot from CoVariants website. Dynamic navigation is available at https://covariants.org/per-country. Green/21 (A/I/J) indicates B.1.617.2 (Delta) sub-lineages. Dark Red (20I) 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 22A indicates Omicron BA.4. Cyan/22D indicates BA.2.75. Bright purple (22E) indicates BQ.1, 22F indicates the recombinant XBB lineage, and Pink/23A indicates XBB.1.5.

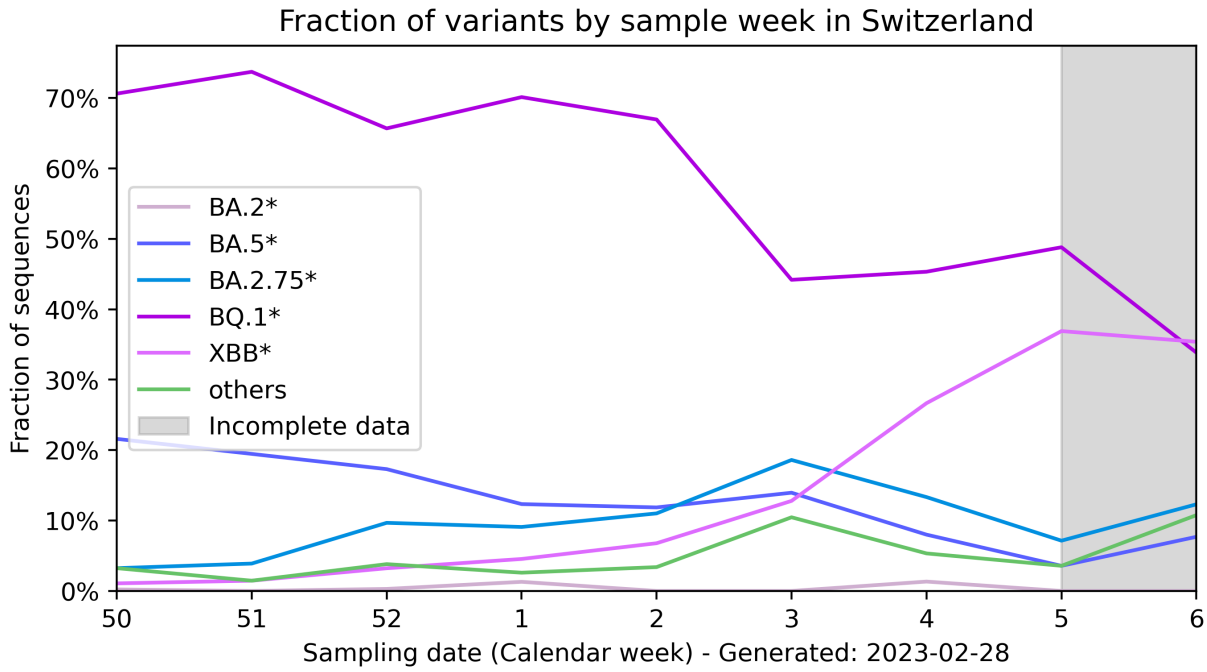
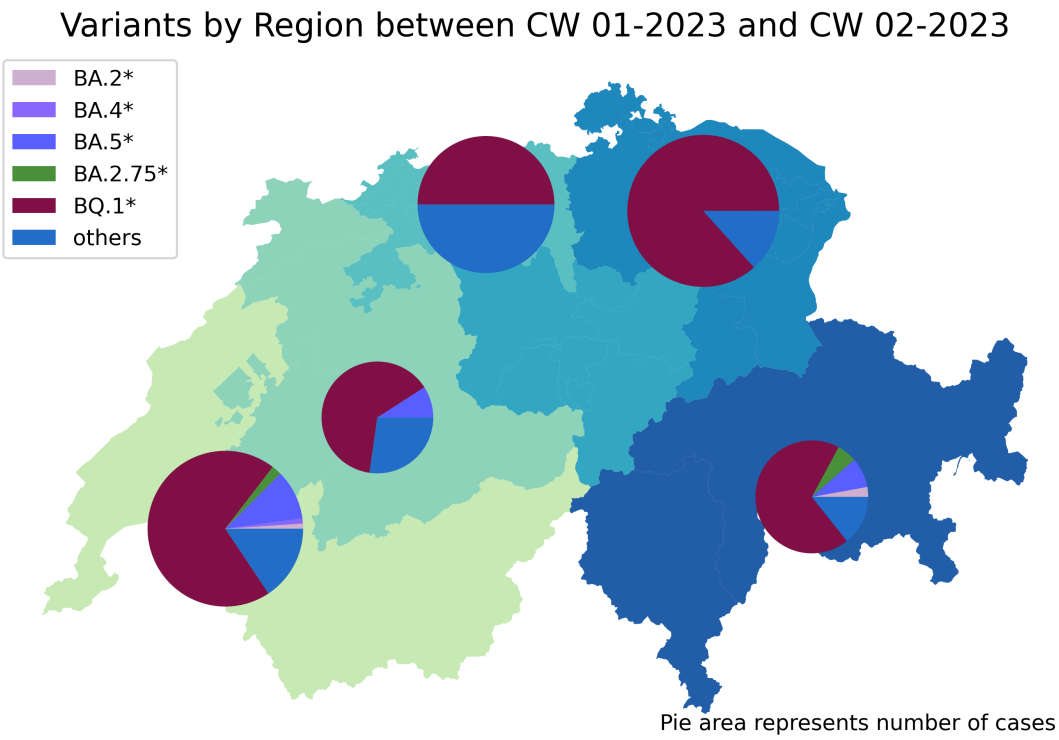


Figure 4: (Left): Percentage of circulating VOCs and VOIs in Switzerland by week, up to week 5 of 2023, according to the sequences from Switzerland that were successfully submitted. Note the grey shaded area indicates a period of incomplete data. Note that as of week 3, while BQ.1 sequences are still the most numerous, they account for less than 50% of the total number of sequences.



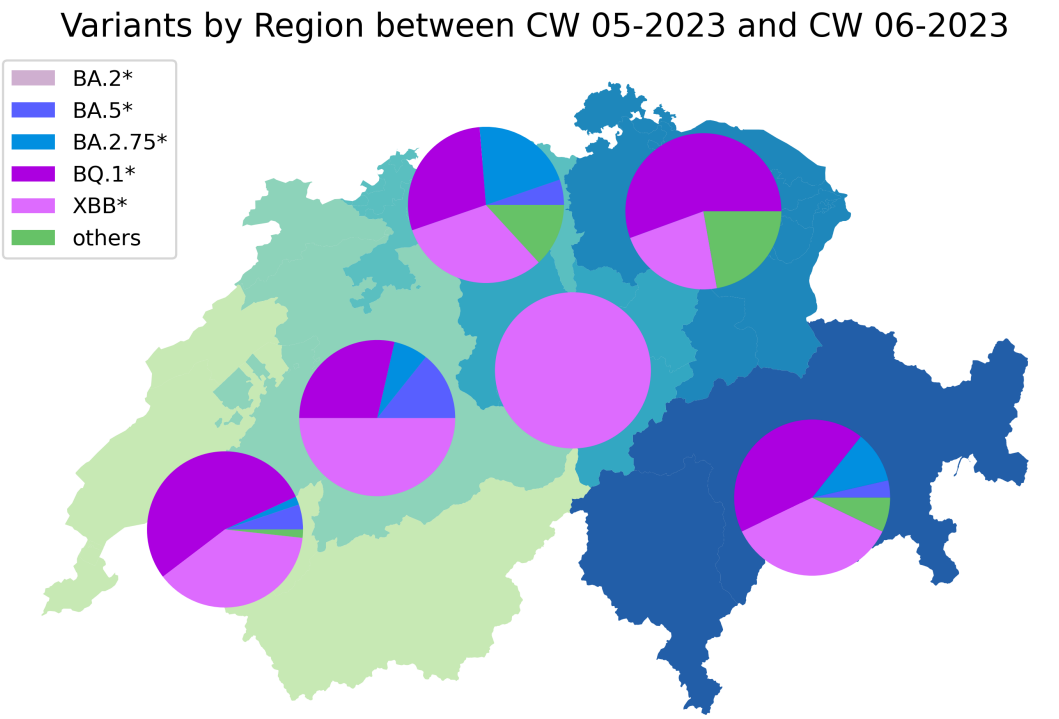


Figure 5: Distribution of variants per region, by Calender Week (CW), for early January 2023 (top) and early February 2023 (bottom) shown on a map. The size of the pie chart corresponds to the total number of sequences (top only). Note the greatly increased share of the XBB lineage and the shrinking share of the share of the BQ.1 lineage.*

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 the recombinant XBB.1.5 lineage will become dominant.

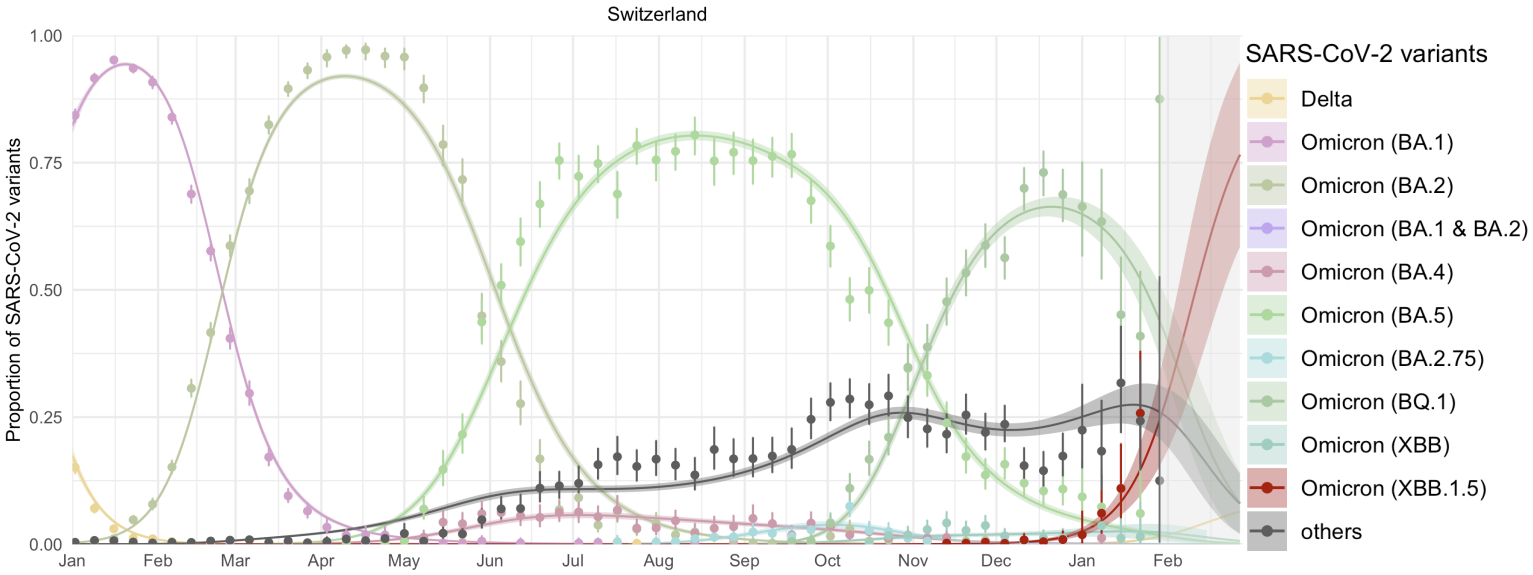


Figure 6: Observed and modeled proportion of SARS-CoV-2 variants over time in Switzerland. Since early 2021, multiple successive variants have been observed to displace all previous variants (often achieving a dominance of >99.9% of the circulation). Alpha was replaced by Delta, followed by Omicron BA.1, then Omicron BA.2, Omicron BA.5, Omicron BQ.1, and now Omicron XBB.1.5. Model fits are based on a multinomial logistic regression with splines.

6. Surveillance of mutations associated with reduced available treatment efficacy

Resistance mutations to available monoclonal antibodies

All sublineages display complete escape from combination of casirivimab/imdevimab. A matched cohort study found a noticeable 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. While the *in vitro* data is clear that sotrovimab does not neutralize BA.2 and later Omicron lineages, clinical data is unclear and there may be a benefit gained from sotrovimab binding to SARS-CoV-2 without neutralizing it. Studies report that both BQ.1.1 and XBB.1.5 strongly escape Sotrovimab, even compared to BA.2 and BA.5.

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.2/4/5 sublineages and/or recombinant lineages lead to complete escape from cilgavimab, and cilgavimab has lost any efficacy that it still had as these sublineages have proliferated. Notably, these lineages include BQ.1.1 which is also reported to be highly resistant to sotrovimab, and XBB.1.5 which is replacing it.

As sotrovimab and tixagevimab/cilgavimab are still being used, additional mutations causing escape from them will thus be closely followed (Table 3).

AA position	World	Europe	Switzerland
Sotrovimab (Spike mutations)			
337	0.03	0.03	0
340	0.09	0.14	0.23 (1 seq)
356	6.22	7.14	4.71
371	94.18	93.16	98.12
377	0.02	0.02	0
449	0.01	0.01	0
476	0.05	0.03	0
494	0.41	0.42	0
Cilgavimab (Spike mutations)			
346	75.24	79.59	83.53
444	50.2	63.62	65.88
445	19.11	10.27	9.18
446	34.32	32.74	19.53
447	0.01	0	0
448	0.01	0 (1 seq)	0
450	1.27	1.5	0.71
452	68.17	76.72	74.59
484	96.24	96.1	99.76
494	0.39	0.42	0
655	98.95	98.68	100
Paxlovid® (Nsp5 mutations)			
48	0.03	0.01	0
49	0.04	0.01	0
140	0.00 (1)	0	0
143	0	0	0
144	0.00 (1)	0 .00(1)	0
165	0.00 (1)	0	0
166	0.00 (1)	0.00 (1)	0
167	0	0	0
168	0.00 (2)	0	0
172	0	0	0
186	0.01 (16)	0.01 (4)	0
188	0.01	0.00 (2)	0
189	0.01 (10)	0.00 (3)	0
192	0.01 (10)	0.00 (1)	0
252	0.00 (8)	0.00 (1)	0

Table 3: Frequency (%) of mutations at residues linked (by deep mutations scanning or other experimental results) to escape from sotrovimab, cilgavimab, or Paxlovid® (5 fold cutoff), January 2023. Numbers in parentheses denote the total number of sequences detected with a given mutation. Note the low number of mutations at sites leading to escape from Paxlovid.

In December, variants with resistance mutations expected to lead to complete escape from both cilgavimab and tixagevimab represented over 92% of the sequences identified in Switzerland. Data for January (shows a proportion of over 95%. **We expect that all available monoclonal antibodies available in Switzerland are currently unable to neutralize the majority of the circulating SARS-CoV-2 viruses.**

Details regarding resistance mutations to the Evushled® components are available below.

In order to get a faster turnaround relative to sequencing, 346T specific PCR was implemented in Geneva. As of week 1, 92.6% of sequences in Geneva which contained this mutation which effectively confers complete escape from Evusheld® neutralization. As the numbers had steadily been climbing, and the vast majority of sequences had this mutation, further PCR testing was stopped as it was deemed unnecessary. Note that other mutations at position 346 as well as 444 also confer complete escape from neutralization by Evusheld®, and the percent of sequences bearing the 346T mutation represent a minimum estimate for the number of sequences corresponding to virus that completely escape neutralization by Evusheld®.

	337 (H, L, R, S, T)		340 (A, D, G, K, Q, V)		356 (T)		371 (F, L)	
Dates	Global	CH/EU	Global	CH/EU	Global	CH/EU	Global	CH/EU
2.1 to 29.1	0.01	0.00/0.01	0.07	0.23/0.12	6.61	4.63/7.06	94.16	97.92/93.18

	377 (K)		449 (N)		476 (S)		494 (P)	
Dates	Global	CH/EU	Global	CH/EU	Global	CH/EU	Global	CH/EU
2.1 to 29.1	0.00	0.00/0.00	0.0	0.00/0.00	0.04	0.00/0.03	0.40	0.00/0.42

Table 4: Percent (to the nearest 0.01%) of Global and Swiss sequences bearing Sotrovimab escape mutations (>5x neutralization drop or >0.8 escape fraction) for January 2023 (2 January to 29 January 2023). Mutated amino acid positions are for the spike protein.

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.

Mutations resulting in partial escape from cilgavimab are shown in table 5. In contrast to the situation with sotrovimab, known mutations enabling escape from Evusheld® increased rapidly in Switzerland and world-wide. During November 2022, variants expected to be completely resistant to Evusheld® (cilgavimab and tixagevimab) made up over 79% of the sequences, and data for January shows a proportion of over 95%. 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.

	346 (I, N, S, T)		444 (E,G,L,M,N,Q,R,S,T)		445 (A)		446 (S)	
Dates	Global	CH/EU	Global	CH/EU	Global	CH/EU	Global	CH/EU
28.11 to 1.1.23	75.22	83.53/79.57	50.2	65.88/63.62	0.95	0.71/0.72	33.9	19.53/32.3

	447 (R, V)		448 (Y)		450 (D, K)		452 (R)	
Dates	Global	CH/EU	Global	CH/EU	Global	CH/EU	Global	CH/EU
28.11 to 1.1.23	0.00	0.00/0.00	0.00	0.00/0.00	1.27	0.71/1.49	67.48	74.35/76.12

	484 (A)		494 (R)		655 (Y)	
Dates	Global	CH/EU	Global	CH/EU	Global	CH/EU
28.11 to 1.1.23	95.64	99.31/95.54	0.00	0.00/0.00	98.94	100/98.65

Table 5: Percent of Global and Swiss sequences bearing cilgavimab escape mutations (>5x neutralization drop or >0.8 escape fraction) for January(2 January 2023 to 29 January 2023). Mutated amino acid positions are for the spike protein

Resistance mutations associated with resistance to other available antivirals

In addition to mAbs, there are other antiviral treatments, such as the 3CL-like protease inhibitor Paxlovid® (PF-07321332, nirmatrelvir/ritonavir) or RNA nucleotide analogues (such as molnupiravir). Given the low proportion of the population that receives Paxlovid®, there appears to be little selection pressure for resistance mutations. Indeed, known escape mutations against Paxlovid® are currently very rare.

Preliminary data confirms that Paxlovid® and remdesivir all retain full *in vitro* efficacy against Omicron sub-lineages. 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. This likely explains the scarcity of escape mutations against Paxlovid®. Notably, while dozens of mutations at sites known to be important for escape from Paxlovid® have been reported worldwide (table 1), few that are actually known to cause escape have been sequenced worldwide during January (table 6), resulting in a miniscule percentage of total sequences. Mutations resulting in partial escape from Paxlovid® are shown below in table 6.

	48 Y		49 I		140 L		143 S	
Dates	Global	CH/EU	Global	CH/EU	Global	CH/EU	Global	CH/EU
2.1 to 29.1	0	0/0	0.00 (1)	0/0	0.0	0/0	0	0/0

	144 A/E/L/P/R/T/V/W		165 K/T		166 A/G/K/V		167 F	
Dates	Global	CH/EU	Global	CH/EU	Global	CH/EU	Global	CH/EU
2.1 to 29.1	0.00 (1)	0/0.00 (1)	0	0/0	0 (1)	0/0 (1)	0	0

	168Δ		172 A/D/E/N/Q/T/Y		186 G		188 S	
Dates	Global	CH/EU	Global	CH/EU	Global	CH/EU	Global	CH/EU
2.1 to 29.1	0	0/0	0	0	0	0/0	0.00 (2)	0/0.00 (1)

	189 K		192 A/E/F/G/H/I/K/L/R/T/Y		252 L	
Dates	Global	CH/EU	Global	CH/EU	Global	CH/EU
2.1 to 29.1	0.00 (1)	0/0.00 (1)	0.00 (2)	0/0 (1)	0.00 (6)	0/0

Table 6: Percent ofGlobal and Swiss counts of sequences bearing >5 fold escape mutations from Paxlovid®: Sequenced escape mutations remained extremely rare worldwide for January 2023 (2 January to 29 January 2023).. Numbers in parentheses indicate the total number of sequences with the mutations. Mutated amino acid positions are for the Nsp5 protein

7. Wastewater surveillance program

As of 2023, the wastewater surveillance program is no longer funded by the national surveillance program, but it continues on an alternate funding source. Data is presented here to be informative, and not to imply that this program is currently part of the national surveillance program.

Sequences are obtained from six wastewater treatment plants (WWTPs) that are tested on a daily basis. At the end of the Month of January, samples from the surveyed treatment plants contained a mixture of BA.5, BQ.1.1, BA.2.75 and XBB*. During the Month of January, XBB* (we do not distinguish between XBB and its subvariants here) grew in relative abundance in the samples from treatment plants in the South and West of the country, becoming the major variant in the samples from Geneva. In those samples, BA.2.75 had a lower relative abundance compared to the samples from Zurich, St-Gallen and Chur, where it was still a highly abundant variant.

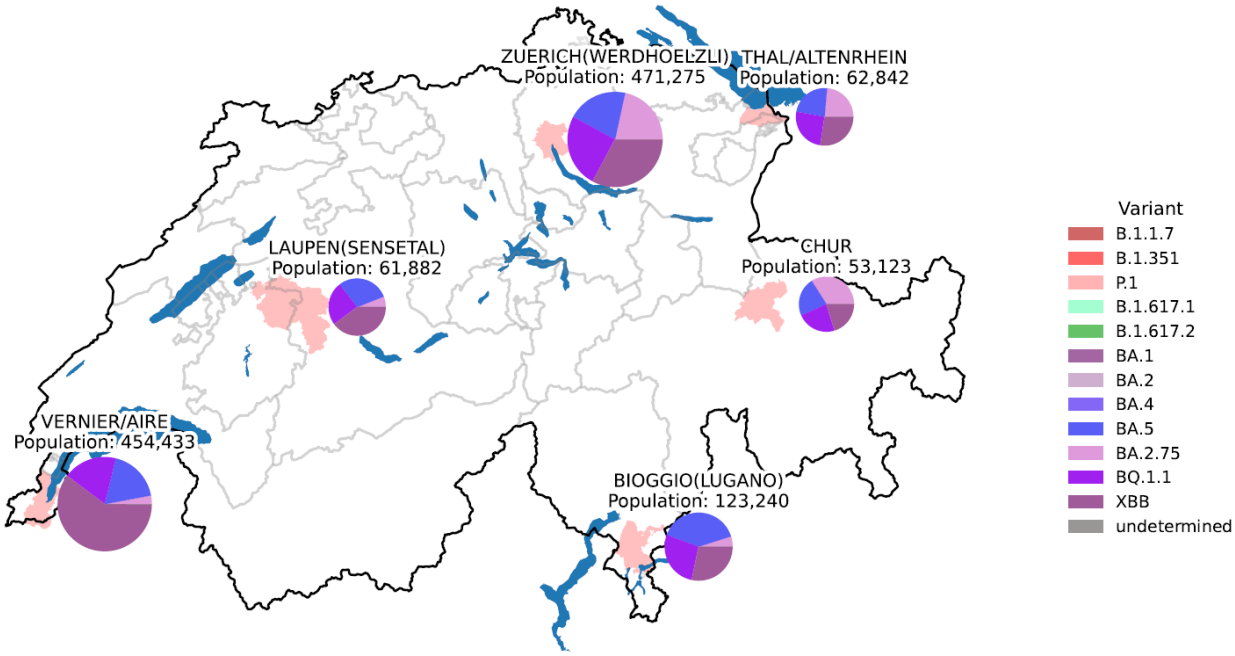


Figure 7:
Overview of the relative abundances of variants of SARS-CoV-2 at the end of December 2022, estimated from wastewater samples collected daily during the month in WWTPs located in 6 different Swiss locations. Pie chart areas are proportional to population connected to the wastewater treatment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

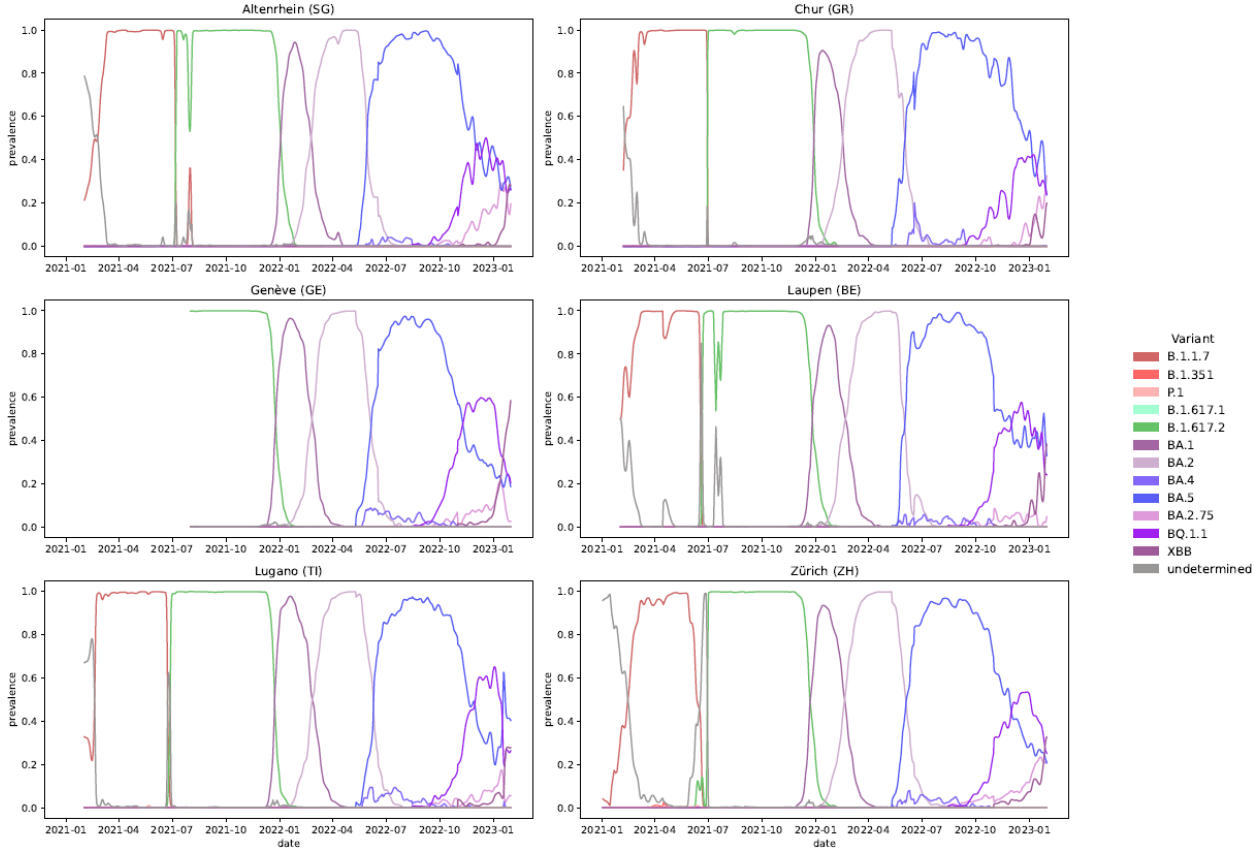


Figure 8: Relative abundances of variants of SARS- CoV-2 estimated from wastewater samples collected daily until January 31, 2023 in WWTPs located in 6 different Swiss cantons. An online dynamic navigation is available at https://bsse.ethz.ch/cbg/research/computational-virology/sarscov2-variants-wastewater-surveillance.html.

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.

sup_table_overview_Jan.xlsx

Supplementary Table 1: Epidemiological data for Switzerland, its regions and cantons for December: 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 sequenced
1	Jan. 2 to Jan. 8	4 882	757	311	41.08
2	Jan. 9 to Jan. 15	3 984	508	0	0
3	Jan. 16 to Jan. 22	3 326	377	196	51.99
4	Jan. 23 to Jan. 29	2 798	256	0	0
	Total	14 990	1 898	507	26.71

Supplementary Table 2: Total number of tests performed by the laboratories participating in the surveillance program from 2 January to 29 January 2023.

Week	Date	EOC	USB	IFIK	CHUV	UZH	ICH-VS	HUG	All
1	Jan. 2 to Jan. 8	38	60	41	63	39	38	32	311
2	Jan. 9 to Jan. 15								
3	Jan. 16 to Jan. 22	40	36	24	18	15	45	18	196
4	Jan. 23 to Jan. 29								
	Total	78	96	65	81	54	83	50	507

*Supplementary Table 3: number of sequences submitted to GISAID by each laboratory during the surveilled period (2 January to 29 January 2023). *including sequencing sent to high-throughput platforms.*

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