Hôpitaux Universitaires Genève

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FACULTÉ DE MÉDECINE

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

Geneva Centre for Emerging Viral Diseases

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Laboratory of virology

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1. Summary

During the month of March, the number of positive tests increased again in Switzerland. This was not associated with any large increase in the number of hospitalizations.

Around 33% of the 5'156 reported positive tests were processed by laboratories participating to the program.

A total of 620 new sequences were submitted to GISAID during the reporting period, covering the month of March (from 27 February to 26 March 2023), which represents around 12% of the positive tests. Note that since the beginning of 2023, the program has been adapted to focus on samples originating from hospitalized patients.

The majority of the sequences in Switzerland still belong to the XBB.1.5 sub-lineage, which results from a recombination between two BA.2 sublineages and additional accumulated mutations. This XBB.1.5 variant replaced the previously circulating BQ.1.1 variant (a derivative of BA.5) in Switzerland during the February and continued to increase in frequency during March. This XBB 1.5 variant exhibits higher affinity for ACE2, and thus 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). It replaced other circulating variants worldwide but is now facing pressure from the related XBB.1.16 variant, which has displaced XBB.1.5 in some areas. 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®) have been dominant (>95% of circulating viruses) since January. All available monoclonal antibodies available in Switzerland are thus unable to effectively neutralize most circulating SARS-CoV-2 viruses, although the change in clinical effectiveness is unclear. 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, David Dreifuss, Chaoran Chen, Tanja Stadler, 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 27 February 2023 to 26 March, 2023 (weeks 9, 10, 11, 12). 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).

On March 15, 2023, WHO updated its definitions for VOCs and VOIs, mainly consisting in making the VOC definition more specific. Greek letters will thus only be assigned to VOCs.

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. These sublineages have successively replaced each other, with the BA.5 sublineage BQ.1 being dominant in most of January, and quickly replaced by the XBB.1.5 variant since mid-February 2023 (see below).

Similarly, highly derived BA.2 sublineages recombinants XBB*, which derive from a recombination event between a BA.2.10 sublineage (BJ.1) and a BA.2.75 sublineage (BM.1.1.1) 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 monoclonal antibodies available on the market.

Notably, the XBB.1.5 sublineage seems to have similar immune escape properties to BQ.1.1, but has a higher ACE2 affinity, presumably enhancing its inherent transmissibility.

In March, 2023, XBB.1.5 was classified as a VOI by WHO. Other XBB sublineages continue to arise, and notably XBB.1.16 has overtaken XBB.1.5 in some parts of the world.

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, such as XBB*. 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.

Severity

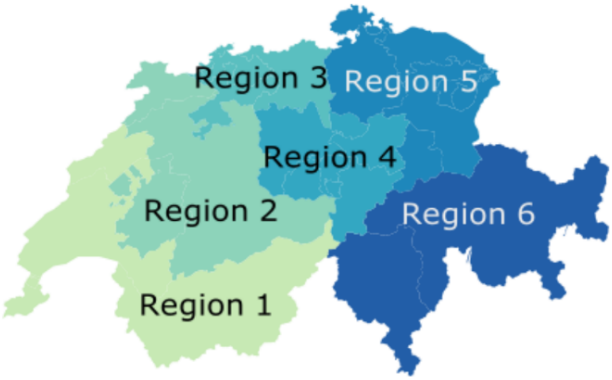
There is currently no evidence that the severity of the new subvariants (such as XBB.1.5 and BQ.1.1,) has significantly changed.

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 March (27 February to 26 March), the FOPH reported a total of 5'156 positive tests (including both RT-PCR and antigen-based tests). Of these, 1'691 (33%) were processed by labs participating in the national surveillance program. After the drop in testing observed since the beginning of the year, the number of positive tests increased all over Switzerland during the month of March. 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 620 SARS-CoV-2 sequences have been declared to have been processed during this period. There are 546 sequences available that were submitted during this period on GISAID (and 634 collected during this period) as of 27 April 2023. This contrast between the numbers of submitted and collected sequences is likely due to reporting delays, which was quite low during the month of March.

The number of sequences collected and submitted during the reporting period represent around 9% of the total of the positive tests.

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
9	February 27-March 5	317
10	March 6-March 12	
11	March 13-March 19	303
12	March 20-March 26	
	Total	620

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 progressively increased again during the month of March 2023 (Calendar weeks 9, 10, 11, and 12). 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.

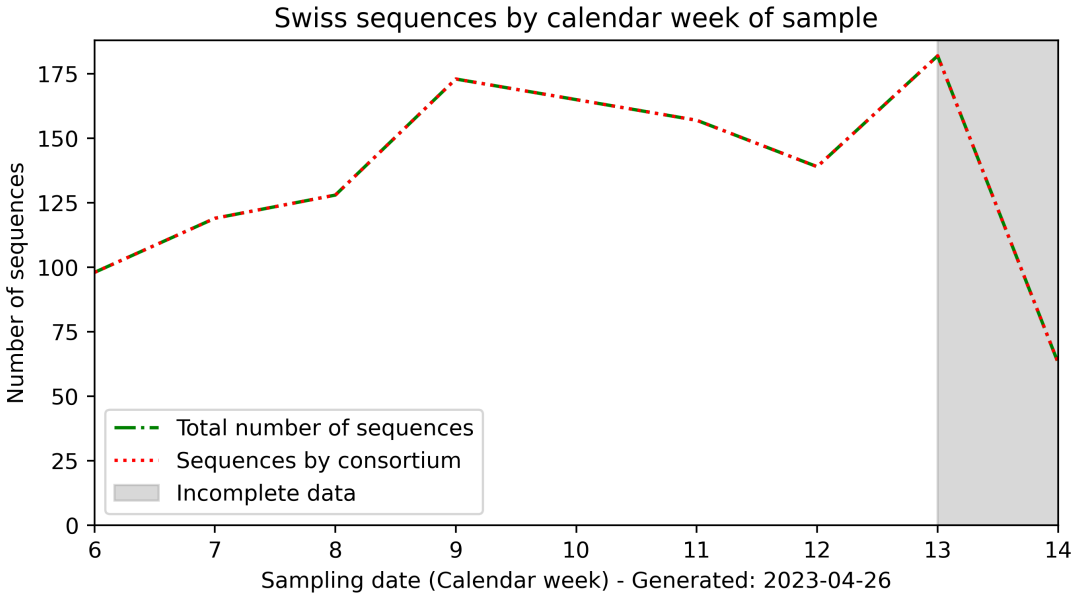


Figure 1: Number of SARS-CoV-2 sequences available for Switzerland (total available Swiss sequences in GISAID in green, Swiss sequences submitted through the program in dotted orange).

Figure 2 displays the number of SARS-CoV-2 cases sequenced for each Swiss region. Notably, region 4 (Luzern, Unterwalden, Uri, Zug and Schwyz) continues to be underrepresented. This reflects the absence of laboratory participating in the program in this region, after the switch of the surveillance towards hospitalized cases.

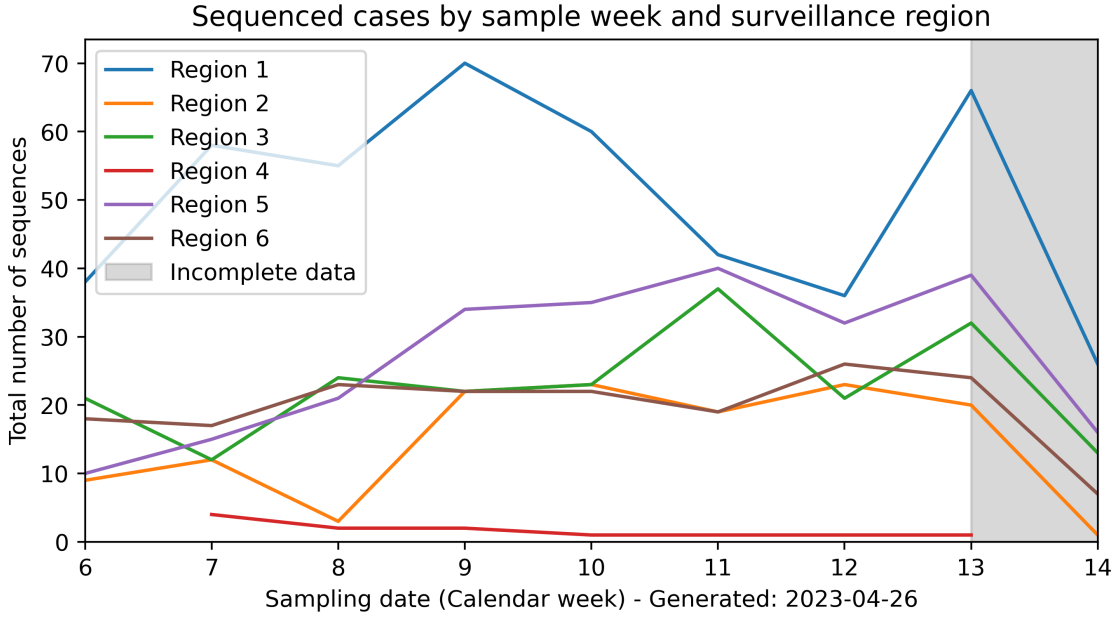


Figure 2: Sequencing coverage among the different Swiss regions per week, by number of sequences.

4. Recently circulating variants in Switzerland

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).

The BQ.1 sublineage (Figures 3-5, Table 4) was replaced by the BA.2 recombinant XBB.1.5 during the month of February. XBB.1.5 continues to dominate. 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, a single XBB.1.16 sequence was detected in Switzerland during March.

Region	BA.2*	BA.2.75*	BA.5*	BQ.1*	XBB*	other	sequences
All	0	34	5	71	471	53	
1	0	10	0	29	160	9	
2	0	6	1	8	68	4	
3	0	7	4	13	74	5	
4	0	0	0	0	3	0	
5	0	4	0	17	90	30	
6	0	7	0	4	73	5	

Table 2: number of sequences corresponding to selected variants in each region of Switzerland from 27 February to 26 March 2023, according to data received by 27 April, 2023.

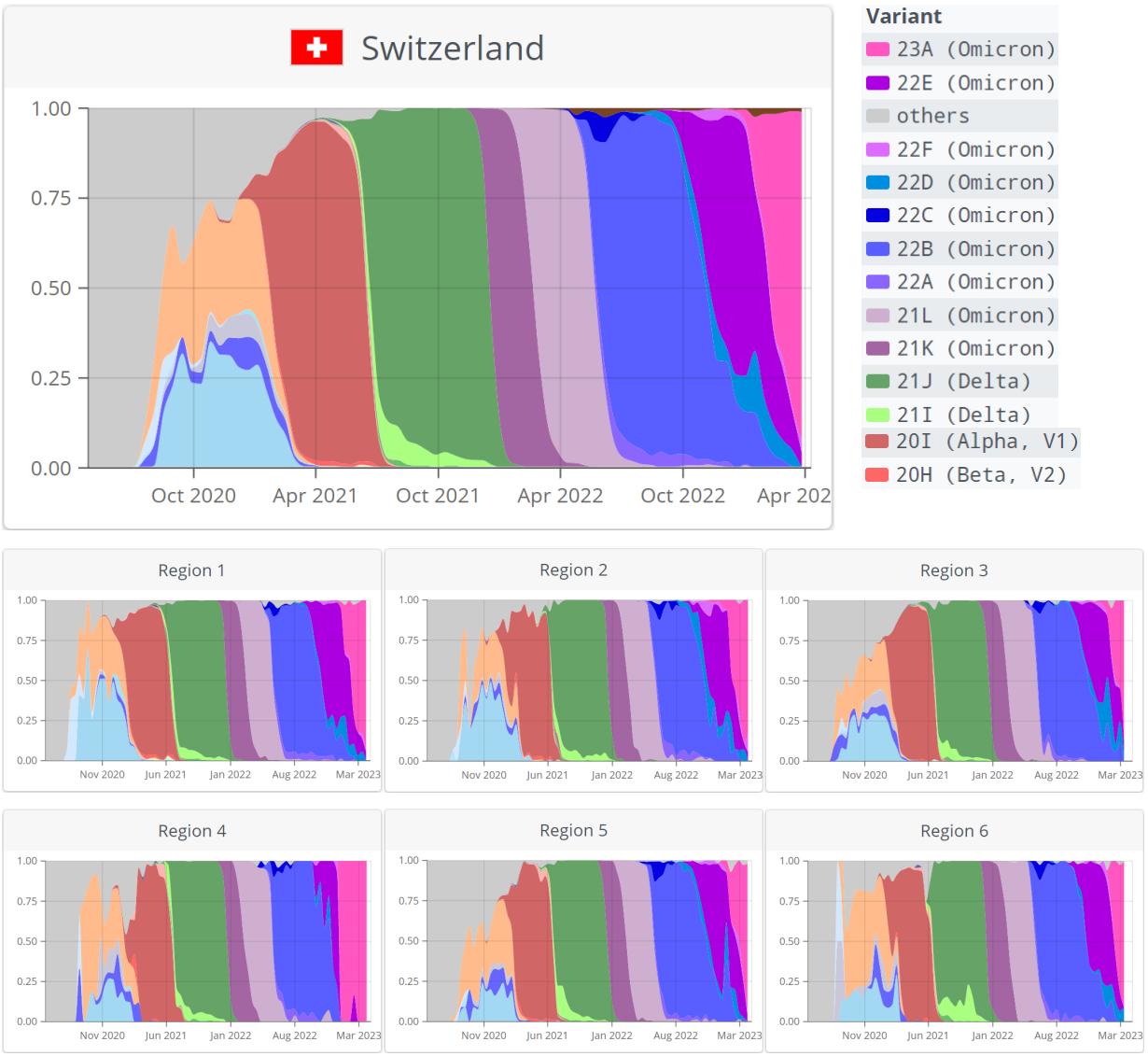


Figure 3: proportion of the total number of sequences (not cases), over time, that fall into defined variant groups, for Switzerland. Screenshot from CoVariants website. Dynamic navigation is available at https://covariants.org/per-country. Green/21 (A/l/J) indicates B.1.617.2 (Delta) sub-lineages. Dark 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.

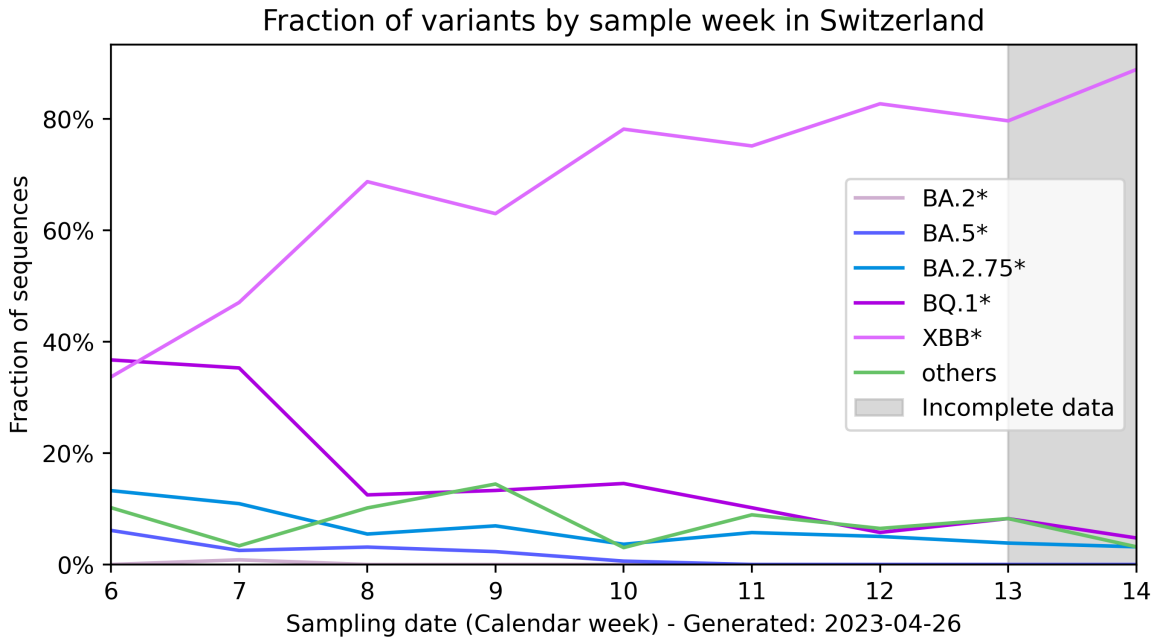


Figure 4: Percentage of circulating VOCs and VOIs in Switzerland by week, up to week 13 of 2023, according to the sequences from Switzerland that were successfully submitted. Note the grey shaded area indicates a period of incomplete data. Note that as of week 6, XBB sequences started to be dominant and represented around 70% of the sequences at the end of the reporting period.

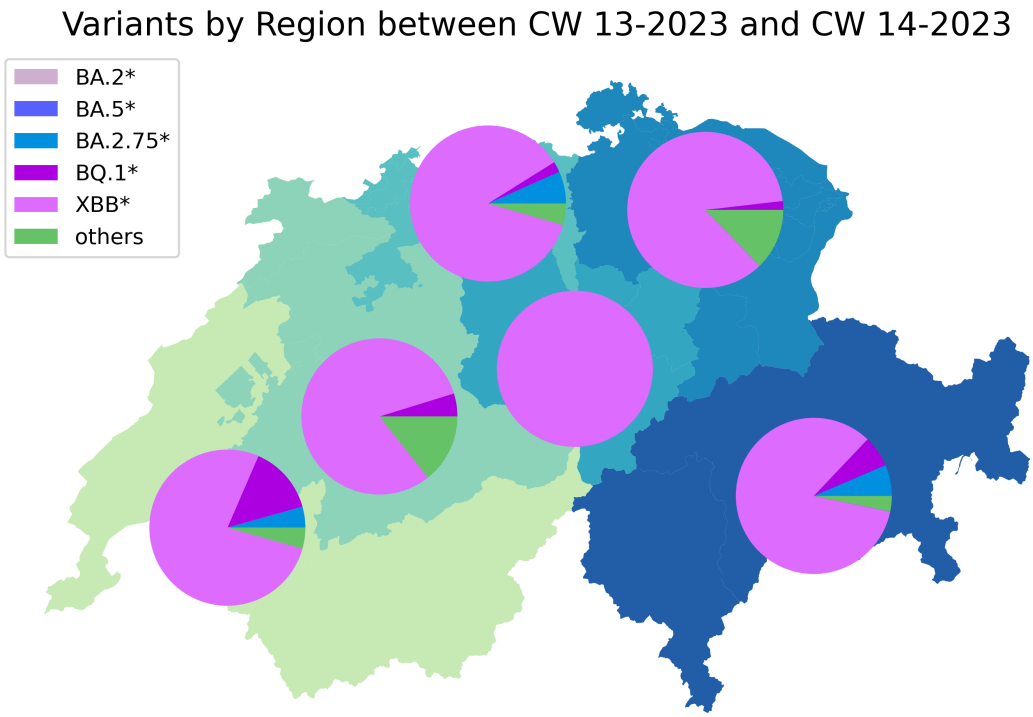


Figure 5: Distribution of variants per region, by Calendar Week (CW), for the end of March 2023. Note the dominance of the XBB lineage

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 2022, the analysis predicted that BA.2 would be displaced by other variants (mainly BA.5), which was indeed correct. The current estimate suggesting that the recombinant XBB.1.5 lineage will become dominant also proves to be correct.

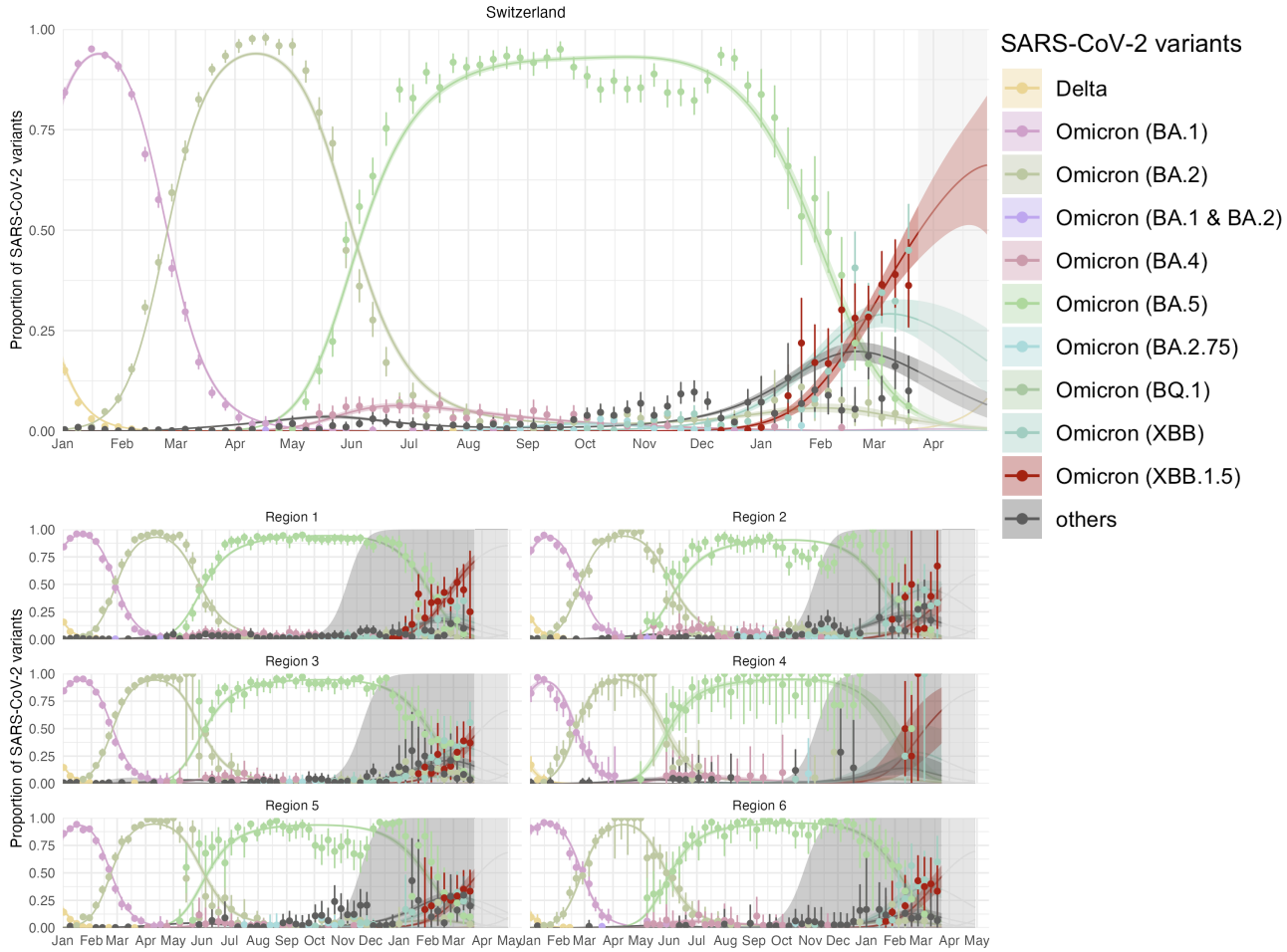


Figure 6: Observed and modeled proportion of SARS-CoV-2 variants over time in Switzerland. Since early 2021, multiple successive variants have been observed to displace all previous variants (often achieving a dominance of >99.9% of the circulation). Alpha was replaced by Delta, followed by Omicron BA.1, 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.

AA position	World	Europe	Switzerland
Sotrovimab (Spike mutations)			
337	0.11	0.04	0
340	0.16	0.08	0
356	4.06	1.53	1.10
371	92.54	91.16	99.21
377	0.13	0.00 (1)	0
449	0.02	0.00 (3)	0
476	0.06	0.02	0
494	0.40	0.25	0.32 (2)
Paxlovid® (Nsp5 mutations)			
48	0.03	0.00 (1)	0
49	0.03	0.00 (2)	0
140	0.00 (1)	0	0
143	0	0	0
144	0.00 (2)	0	0
165	0	0	0
166	0	0	0
167	0	0	0
168	0	0	0
172	0	0	0
186	0.01 (8)	0.00 (2)	0
188	0.01 (11)	0.00 (1)	0
189	0.01 (11)	0	0
192	0.01 (14)	0	0
252	0.00 (6)	0.00 (1)	0

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, and that additional spike 346 mutations seen in BA.2/4/5 sublineages and/or recombinant lineages such as BQ.1.1 and XBB.1.5 lead to complete escape. Since January 2023, variants with resistance mutations expected to lead to complete escape from both cilgavimab and tixagevimab represented over 95% of the sequences identified in Switzerland.

Mutations causing escape from mAbs are closely followed (Table 3).

Table 3: Frequency (%) of mutations at residues linked (by deep mutations scanning or other experimental results) to escape from sotrovimab, or Paxlovid® (5 fold cutoff), February 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. Note, both BA.5 and BA.2 (including recombinants such as XBB and XBB 1.5) contain the spike S371F mutation leading to Sotrovimab resistance.*

Resistance mutations associated with resistance to other available antivirals

Other antivirals are available in Switzerland: the 3CL-like protease inhibitor Paxlovid® (PF-07321332, nirmatrelvir/ritonavir) or RNA nucleotide analogues (such as remdesivir).

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 3), few that are actually known to cause escape have been sequenced worldwide during March, resulting in a miniscule percentage of total sequences.

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. In February, the waste water program expanded from 6 sampling centers to 9, in March it increased to 10.

During the Month of March, the XBB* variant grew in relative abundance in the samples from all treatment plants across the country, reaching around 90% relative abundances in all of the sampled treatment plants. The remaining sequenced RNA was found to belong mainly to BA.2.75 and BQ.1.1. As of now, we are not distinguishing between XBB* subvariants.

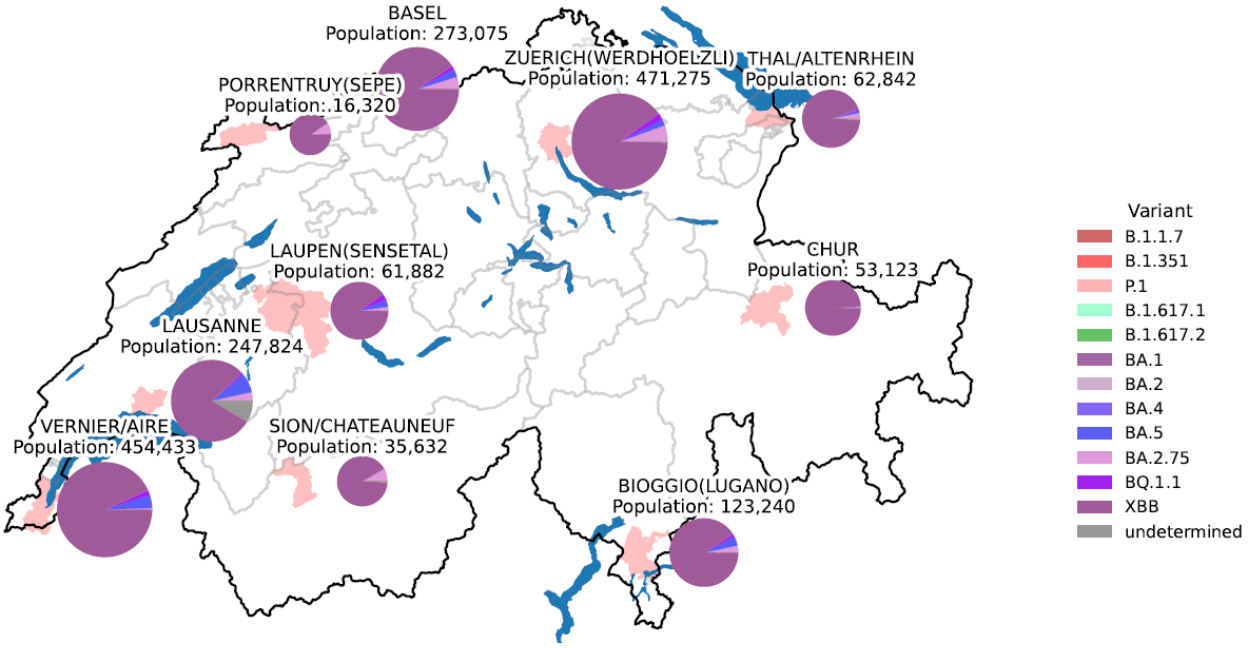


Figure 7: Overview of the relative abundances of variants of SARS-CoV-2 at the end of March 2023, estimated from wastewater samples collected daily in WWTPs located at 9 different Swiss locations. The size of the pie charts are proportional to the population connected to the wastewater treatment plants. Pink shaded areas represent catchment areas (boundaries from 2017). The population connected to the Vernier (GE) wastewater treatment plant also includes ~44,000 inhabitants from neighbouring French communities

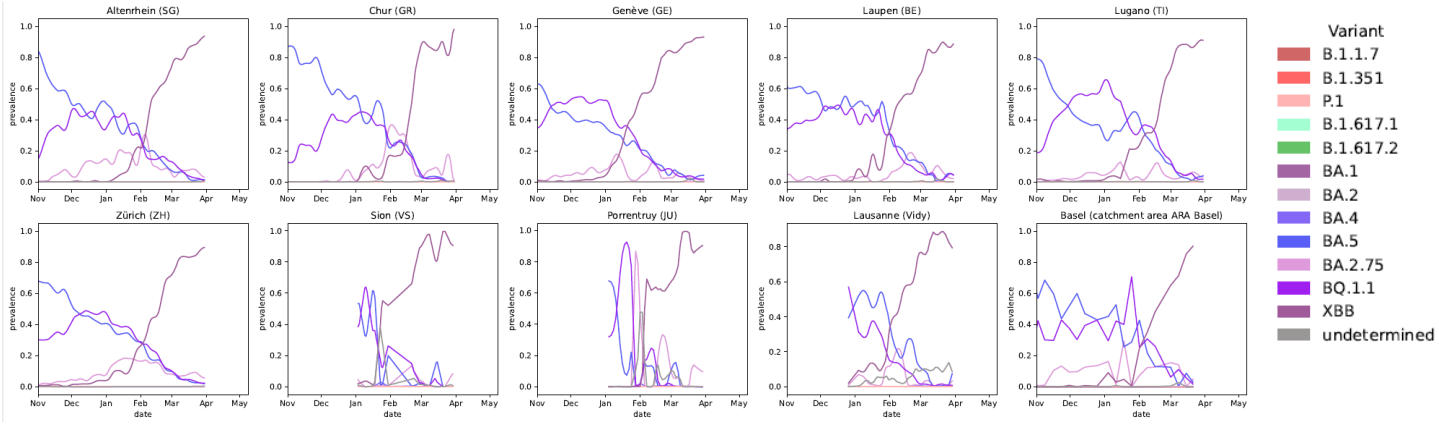


Figure 8: Relative abundances of variants of SARS- CoV-2 estimated from wastewater samples collected daily until February 28, 2023 in WWTPs from 9 different Swiss locations. An online dynamic navigation is available at https://cov-spectrum.org/stories/wastewater-in-switzerland

Acknowledgements:

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

We would also like to thank the CoVICIS project (https://covicis.eu/) for supplementary funding for genomic sequencing in Geneva.

Erik Boehm, Marc Friedli, Pauline Vetter, Samuel Cordey, Richard Neher, Christian Althaus, Emma Hodcroft, Tanja Stadler, Philippe Lemercier, Ioannis Xenarios, Lorenzo Cerutti, Louis Du Plessis, Erik Studer, Laurent Kaiser, for the Swiss national SARS-CoV-2 genomic and variants surveillance program coordination committee.

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.

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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
9	February 27-March 5	2 350	371	317	38.7
10	March 6-March 12	2 605	448		
11	March 13-March 19	2 495	434	303	34.7
12	March 20-March 26	2 164	438		
	Total	9 614	1 691	620	36.7

Supplementary Table 2: Total number of tests performed by the laboratories participating in the surveillance program from 27 February to 26 March 2023.

week	date	HUG	CHUV	ICH-VS	IFIK	UZH IMV	USB	EOC	All
9	February 27-March 5	60	46	21	27	73	50	40	317
10	March 6-March 12								
11	March 13-March 19	49	38	23	34	68	54	37	303
12	March 20-March 26								
	Total	109	84	44	61	141	104	77	620

Supplementary Table 3: number of sequences submitted to GISAID by each laboratory during the surveilled period (27 February to 26 March 2023).

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